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 Brentuximab Vedotin (new therapeutic indication: Hodgkin lymphoma, first line)

of 5 September 2019

At its session on 5 September 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. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of brentuximab vedotin in accordance with the resolution of 5 July 2018:

Brentuximab vedotin

Resolution of: 5 September 2019
Entry into force on: 5 September 2019
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 6 February 2019):

ADCETRIS® is indicated for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD) (see sections 4.2 and 5.1).

1. Extent of the additional benefit of the medicinal product

Brentuximab vedotin is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO). This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL)

Extent of the additional benefit of brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine:

Non-quantifiable

Study results according to endpoints:[1]

Adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL)

ECHELON-1 open Phase III study (data cut-off of 20 April 2017):

Brentuximab vedotin + doxorubicin + vinblastine + dacarbazine (A + AVD) vs

Doxorubicin + bleomycin + vinblastine + dacarbazine (ABVD)

Mortality

Endpoint	**A + AVD**		**ABVD**		A + AVD vs ABVD
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*	Hazard ratio[b] [95% CI] p value Absolute difference (AD)[a]
Overall survival (OS)					
	425[c]	n.a. [n.a.; n.a.] *14 (3)*	421[c]	n.a. [n.a.; n.a.] *26 (6)*	0.52 [0.27; 0.995] 0.044

Morbidity

Endpoint	**A + AVD**		**ABVD**		A + AVD vs ABVD
	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*	Hazard ratio[d] [95% CI] p value Absolute difference (AD)[a]
Modified progression-free survival (mPFS)[e]					
	425[c]	n.a. [n.a.; n.a.] *77 (18)*	421[c]	n.a. [n.a.; n.a.] *102 (24)*	0.71 [0.53; 0.96] 0.023

[1] Data from the dossier evaluation by the G-BA (published on 17 June 2019) as well as the amendment to the dossier evaluation of the G-BA (published on 5 September 2019) unless indicated otherwise.

Endpoint	A + AVD		ABVD		A + AVD vs ABVD
	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*	Effect estimate [95% CI] p value Absolute difference (AD)[a]
Relapse-free survival (RFS)					
	335[g]	n.a. [n.a.; n.a.] *40 (12)*	327[g]	n.a. [n.a.; n.a.] *60 (18)*	HR: 0.64[b] [0.43; 0.96] 0.031 RR: 0.65 [0.45; 0.94] 0.021[h]

Endpoint	A + AVD		ABVD		A + AVD vs ABVD
	N	Mean [SD]	N	Mean [SD]	Mean difference [95% CI] p value[i]
Health status (EQ-5D VAS)[j]					
End of Treatment (EoT) visit	425[c]	73.96 [20.76]	421[c]	76.70 [18.96]	−2.74 [−5.63; 0.14] 0.062
9 months after EoT	425[c]	82.38 [19.96]	421[c]	82.28 [17.01]	0.11 [−2.92; 3.13] 0.945

Endpoint	A + AVD		ABVD		A + AVD vs ABVD
	N	Mean [SD]	N	Mean [SD]	Mean difference[k] [95% CI] p value[i]
Symptomology (EORTC QLQ-C30) – change from baseline[l]					
Fatigue scale					
End of Treatment (EoT) visit	425[c]	−8.12 [30.76]	421[c]	-14.42 [27.41]	6.18 [2.99; 9.37] <0.001 Hedges' g 0.28 [0.14; 0.43]
9 months after EoT	425[c]	−20.00 [29.22]	421[c]	-19.17 [28.79]	-0.68 [−3.84; 2.47] 0.670
Pain scale					
End of Treatment (EoT) visit	425[c]	−8.56 [29.68]	421[c]	-12.28 [28.55]	5.02 [2.05; 7.99] <0.001 Hedges' g 0.25 [0.10; 0.39]
9 months after EoT	425[c]	-14.86 [29.10]	421[c]	-13.03 [28.79]	−0.77 [−3.80; 2.26] 0.619
Nausea and vomiting scale					
End of Treatment (EoT) visit	425[c]	-1.64 [17.76]	421[c]	−4.11 [17.42]	1.72 [0.10; 3.34] p = 0.037 Hedges' g 0.16 [0.01; 0.30]
9 months after EoT	425[c]	−4.07 [14.95]	421[c]	−4.67 [17.90]	-0.43 [−2.07; 1.22] 0.610
Item dyspnoea					
End of Treatment (EoT) visit	425[c]	−5.83 [30.46]	421[c]	−4.54 [30.69]	-2.29 [−5.43; 0.86] 0.154
9 months after EoT	425[c]	-10.66 [27.67]	421[c]	-10.07 [28.70]	-2.34 [−5.07; 0.39] 0.093

(Continuation)

Endpoint	A + AVD		ABVD		A + AVD vs ABVD
	N	Mean [SD]	N	Mean [SD]	Mean difference[k] [95% CI] p value[i]
Loss of appetite scale					
End of Treatment (EoT) visit	425[c]	-14.98 [29.67]	421[c]	-15.24 [32.94]	1.47 [-1.32; 4.26] 0.303
9 months after EoT	425[c]	-18.31 [29.80]	421[c]	-17.76 [30.93]	−0.54 [−2.97; 1.89] 0.660
Item sleeplessness					
End of Treatment (EoT) visit	425[c]	-12.93 [36.55]	421[c]	-18.19 [36.07]	4.20 [0.55; 7.86] 0.024 Hedges' g 0.17 [0.02; 0.31]
9 months after EoT	425[c]	-19.05 [32.82]	421[c]	-17.99 [34.46]	-1.83 [−5.42; 1.76] 0.317
Item constipation					
End of Treatment (EoT) visit	425[c]	−4.30 [28.04]	421[c]	−4.80 [25.85]	0.16 [−2.58; 2.90] 0.911
9 months after EoT	425[c]	−7.05 [24.74]	421[c]	−7.38 [25.45]	-1.07 [−3.39; 1.25] 0.365
Item diarrhoea					
End of Treatment (EoT) visit	425[c]	−2.85 [21.77]	421[c]	0.00 [20.70]	−2.09 [−4.26; 0.08] 0.059
9 months after EoT	425[c]	−3.54 [20.47]	421[c]	−0.12 [19.58]	-2.98 [−5.23; −0.74] 0.009 Hedges' g −0.22 [−0.38; −0.05]

Health-related quality of life

Endpoint	A + AVD		ABVD		A + AVD vs ABVD
	N	Mean [SD]	N	Mean [SD]	Mean difference[k] [95% CI] p value[i]
EORTC QLQ-C30 – change from baseline[m]					
Global scale of global health status/quality of life					
End of Treatment (EoT) visit	425[c]	5.92 [24.05]	421[c]	10.40 [23.70]	-4.43 [−7.01; −1.85] < 0.001 Hedges' g -0.25 [−0.40; −0.11]
9 months after EoT	425[c]	16.24 [22.86]	421[c]	14.62 [23.13]	1.75 [−0.90; 4.40] 0.196
Physical function scale					
End of Treatment (EoT) visit	425[c]	-1.72 [22.59]	421[c]	5.44 [20.56]	-6.59 [−9.05; −4.12] <0.001 Hedges' g −0.39 [−0.54; −0.24]
9 months after EoT	425[c]	7.45 [20.12]	421[c]	9.08 [19.60]	-0.99 [−3.13; 1.15] 0.363
Scale role function					
End of Treatment (EoT) visit	425[c]	1.96 [34.65]	421[c]	10.34 [32.29]	−9.09 [−12.71; −5.47] <0.001 Hedges' g -0.37 [−0.51; −0.22]
9 months after EoT	425[c]	16.16 [32.48]	421[c]	14.71 [32.16]	0.48 [−2.73; 3.69] 0.770
Emotional function scale					
End of Treatment (EoT) visit	425[c]	7.32 [22.02]	421[c]	7.61 [19.51]	-1.44 [−3.95; 1.06] 0.259
9 months after EoT	425[c]	13.00 [23.53]	421[c]	8.36 [21.30]	2.31 [−0.52; 5.15] 0.110

(Continuation)

Endpoint	A + AVD		ABVD		A + AVD vs ABVD
	N	Mean [SD]	N	Mean [SD]	Mean difference[k] [95% CI] p value[i]
Cognitive function scale					
End of Treatment (EoT) visit	425[c]	-1.51 [21.03]	421[c]	-1.02 [20.60]	0.91 [−3.48; 1.65] 0.485
9 months after EoT	425[c]	2.91 [19.59]	421[c]	−0.40 [21.04]	3.06 [0.39; 5.73] 0.025 Hedges' g 0.19 [0.02; 0.35]
Social function scale					
End of Treatment (EoT) round	425[c]	−0.37 [30.24]	421[c]	6.89 [29.13]	-8.50 [−11.96; −5.03] < 0.001 Hedges' g -0.36 [−0.51; −0.21]
9 months after EoT	425[c]	11.76 [27.05]	421[c]	10.80 [29.88]	0.10 [−3.16; 3.36] 0.952

Side effects

Endpoint	A + AVD		ABVD		A + AVD vs ABVD
	N	Patients with event n *(%)*	N	Patients with event n *(%)*	Relative risk [95% CI] p value[n]
Adverse events (AE) in total					
	424[o]	416 *(98)*	413[o]	403 *(98)*	-
Serious adverse events (SAE)					
	424[o]	170 *(40)*	413[o]	114 *(28)*	1.45 [1.20; 1.77] 0.00014
AE (CTCAE grade ≥ 3)					
	424[o]	352 *(83)*	413[o]	278 *(67)*	1.23 [1.14; 1.34] < 0.0001

(Continuation)

Endpoint	**A + AVD**		**ABVD**		A + AVD vs ABVD
	N	Patients with event n *(%)*	N	Patients with event n *(%)*	Relative risk [95% CI] p value[n]
Discontinuation of ≥ 1 component of the study medication because of AE					
	424[o]	44 *(10)*	413[o]	66 *(16)*	0.65 [0.46; 0.93] 0.01651
AE with CTCAE grade ≥ 3 with incidence ≥ 1% in one study arm and statistical significance to level p ≤ 0.05 at the SOC level					
Blood and lymphatic system disorders	424[o]	279 *(66)*	413[o]	197 *(48)*	1.38 [1.22; 1.56] < 0.0001
Investigations	424[o]	85 *(20)*	413[o]	152 *(13)*	1.59 [1.16; 2.19] 0.0036
Infections and infestations	424[o]	72 *(17)*	413[o]	44 *(11)*	1.59 [1.12; 2.26] 0.0081
Gastrointestinal disorders	424[o]	64 *(15)*	413[o]	20 *(5)*	3.12 [1.92; 5.06] < 0.0001
Nervous system disorders	424[o]	47 *(11)*	413[o]	18 *(4)*	2.54 [1.50; 4.30] 0.0003
Metabolism and nutrition disorders	424[o]	24 *(6)*	413[o]	12 *(3)*	1.95 [0.99; 3.84] 0.0497
Musculoskeletal and connective tissue disorders	424[o]	14 *(3)*	413[o]	2 *(0.5)*	6.82 [1.56; 29.8] 0.0029
Psychiatric disorders	424[o]	10 *(2)*	413[o]	2 *(0.5)*	4.87 [1.07; 22.1] 0.0227

(Continuation)

Endpoint	**A + AVD**		**ABVD**		A + AVD vs ABVD
	N	Patients with event n *(%)*	N	Patients with event n *(%)*	Relative risk [95% CI] p value[n]
SAE with incidence ≥ 5% in one study arm (SOC; *PT*) and statistical significance to level p ≤ 0.05					
Blood and lymphatic system disorders	424[o]	85 *(20)*	413[o]	32 *(8)*	2.59 [1.76; 3.80] < 0.0001
Febrile neutropenia	424[o]	71 *(17)*	413[o]	29 *(7)*	2.39 [1.58; 3.59] < 0.0001
Gastrointestinal disorders	424[o]	37 *(9)*	413[o]	16 *(4)*	2.25 [1.27; 3.99] 0.0040
AE of special interest (CTCAE grade ≥ 3 and SAE) and statistical significance to level p ≤ 0.05					
Interstitial lung disease (SMQ)					
CTCAE grade ≥ 3	424[o]	4 *(<1)*	413[o]	13 *(3)*	0.30 [0.10; 0.91] 0.0239
SAE	424[o]	4 *(<1)*	413[o]	12 *(3)*	0.33 [0.11; 0.999] 0.0383
Any peripheral neuropathy (SMQ)					
CTCAE grade 3	424[o]	40 *(9)*	413[o]	8 *(2)*	4.87 [2.31; 10.28] 0.0001
Peripheral motor neuropathy (SSQ)					
CTCAE grade 3	424[o]	12 *(3)*	413[o]	0	n.c. 0.0006
Peripheral sensory neuropathy (SSQ)					
CTCAE grade 3	424[o]	36 *(8)*	413[o]	8 *(2)*	4.38 [2.06; 9.32] < 0.0001
Neutropenia (PT neutropenia and PT reduced neutrophil number)					
CTCAE grade 4	424[o]	200 *(47)*	413[o]	113 *(27)*	1.72 [1.43; 2.08] < 0.0001
SAE	424[o]	18 *(4)*	413[o]	2 *(<1)*	8.77 [2.05; 37.54] 0.0004

(Continuation)

Endpoint	**A + AVD**		**ABVD**		A + AVD vs ABVD
	N	Patients with event n *(%)*	N	Patients with event n *(%)*	Relative risk [95% CI] p value[n]
Febrile neutropenia (PT)					
CTCAE grade 3	424[o]	56 *(13)*	413[o]	25 *(6)*	2.18 [1.39; 3.43] 0.0005
CTCAE grade 4	424[o]	24 *(6)*	413[o]	10 *(2)*	2.34 [1.13; 4.83] 0.0177
SAE	424[o]	71 *(17)*	413[o]	29 *(7)*	2.39 [1.58; 3.59] < 0.0001
Neutropenia of severity 3 or 4 with infection					
	424[o]	96 *(23)*	413[o]	60 *(15)*	1.56 [1.16; 2.09] 0.0026

a) Absolute difference (AD) given only in the case of a statistically significant difference; own calculation.
b) Hazard ratio and 95% CI based on Cox regression model stratified by region and number of IPFP risk factors. p value based on stratified log rank test.
c) ITT population of the subgroup of Stage IV (population compliant with marketing authorisation)
d) Hazard Ratio and 95% CI based on unstratified Cox regression model. p value based on unstratified log rank test.
e) Time from randomisation to first documentation of progressive disease, death of any cause, or in patients with incomplete response in accordance with IRF: the receipt of subsequent antineoplastic chemo- or radiotherapy for HL (second-line treatment) after scheduled completion of first-line treatment.
f) Number of patients who had CR at the end of first-line treatment; subgroup of Stage IV.
g) Proportion of patients with CR of the subgroup with stage IV.
h) Chi-square test
i) t test; two-sided p value
j) Higher values mean a better health status.
k) LS mean difference based on mixed linear model with repeated measurements (independent variables (fixed effects): treatment group, study round, interaction term between treatment group and study round, baseline value, interaction term between baseline value and study round and the stratification factors region and number of IPFP risk factors). Only measured values for EoT and 9 months after EoT are considered in the model.
l) Higher values mean a worse symptomology
m) Higher values mean a better quality of life
n) Mantel-Haenszel Chi-square test
o) Security population of the subgroup of Stage IV (population compliant with marketing authorisation)

Abbreviations used:
AD = absolute difference; A+ AVD = brentuximab vedotin + doxorubicin + vinblastine + dacarbazine; ABVD = doxorubicin + bleomycin + vinblastine + dacarbazine; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 Item; EoT = End of Treatment round; EQ-5D VAS = EuroQol-5-Dimensions visual analogue scale; HL = Hodgkin lymphoma; HR = hazard ratio; IRF = independent review facility; CI = confidence interval; mPFS = modified progression-free survival; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; OS = overall survival; PT = preferred term; RR = relative risk; SD = standard deviation; SMQ = standardised MedDRA query; SOC = system organ class; SSQ = standardised search query; SAE = serious adverse event; AE = adverse event; vs = versus

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

Adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL)

approx. 220–380 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 Adcetris® (active ingredient: brentuximab vedotin) at the following publicly accessible link (last access: 12 June 2019):

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

Treatment with brentuximab vedotin should only be initiated and monitored by specialists in internal medicine, haematology, and oncology experienced in the treatment of patients with Hodgkin lymphoma.

This medicinal product was authorised under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

4. Treatment costs

Annual treatment costs:

Adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL)

Designation of the therapy	Annual treatment costs/patient
Brentuximab vedotin	€ 85,277.04
Doxorubicin	€ 1,530.16
Vinblastine	€ 3,036.24
Dacarbazine	€ 1,600.08
Total	€ 91,443.52
Additionally required SHI services	
Pegfilgrastim (G-CSF prophylaxis)	€ 7,212.24

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2019

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ Unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Brentuximab vedotin	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	2	12	€ 852
Doxorubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	12	€ 972
Vinblastine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	12	€ 972
Dacarbazine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	12	€ 972

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 5 September 2019.

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

Berlin, 5 September 2019

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

Prof Hecken