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
Brentuximab vedotin

from 16 May 2013

In its session on 16 May 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 18 April 2013 (Federal Gazette, AT 13.06.2013 B2), as follows:

I.

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

Brentuximab vedotin

Therapeutic indication:

Adcetris® is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):

1. following autologous stem-cell transplant (ACST) or

2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

Adcetris® is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

1. Extent of additional benefit of the pharmaceutical

Brentuximab vedotin is authorized as a pharmaceutical for the treatment of a rare disease (orphan drug) in accordance with EC regulation number 141/2000 of the European Parliament and Council of 16 December 1999 on orphan drugs. In accordance with section 35a, paragraph 1, sentence 10, the additional medical benefit has been proved through market authorization.

In accordance with the rules of procedure of the Federal Joint Committee, chapter 5, section 12, paragraph 1, number 1, sentence 2, the Federal Joint Committee determines the extent of the additional benefit for the number of patients and patient groups for whom a therapeutically significant additional benefit exists. This quantification of the additional benefit has been conducted in accordance with the criteria laid out in the rules of procedure, chapter 5, section 5, paragraph 7, numbers 1 to 4.

Extent of additional benefit:

a) Treatment of relapsed or refractory CD30+ Hodgkin lymphoma following autologous stem-cell transplant:

Not quantifiable

Study results according to endpoints[1]:

Brentuximab vedotin Study SG035-0003	
Mortality	
Overall survival[2]	
Data cut-off 16 September 2010	
N = 102	Number of patient deaths, n = 13 (13%); Median overall survival[3] [95% CI] = not achieved [n.a.]

[1] Data from the SG035-0003 study from the G-BA benefit assessment of 1 March 2013.

[2] Intention to treat (ITT) assessment

[3] Median overall survival/progression-free or incident-free survival (in months) were estimated using the Kaplan-Meier method

Brentuximab vedotin Study SG035-0003	
Data cut-off 7 October 2010	
N = 102	Number of patient deaths, n = 36 (35 %); Median overall survival[3] [95% CI] = 27.0 months [23.9; n.a.]
Data cut-off 2 April 2012	
N = 102	Number of patient deaths, n = 40 (39 %); Median overall survival[3] [95% CI] = not achieved [27; n.a.]
Morbidity	
Progression-free survival[2] (time from start of treatment until initial documentation of objective tumour progression or death, data cut-off 16 September 2010)	
N = 102	n[4] = 64 (63%); Median[3] [95% CI] = 25.1 weeks [21.9; 39.1]
Incident-free survival[2] (time from start of study treatment until each treatment failure, including disease progression or interruption of treatment for any reason, e.g. toxicity, patient preference, initiation of a new treatment other than stem-cell transplant without documented progression or death, data cut-off 16 September 2010)	
N = 102	n[5] = 81 (79 %); Median[3] [95% CI] = 29.0 weeks [23.9; 38.3]
Objective response rate[2] (percentage of patients who achieved complete or partial remission within observation period)	
N = 102	n = 76 (75%); [95% CI] = [64.9; 82.6]
Complete remission[2] (percentage of patients with complete remission within observation period)	
N = 102	n = 35 (34%); [95% CI] = [25.2; 44.4]
B symptoms remission rate[2] (percentage of patients with lymphoma-associated B symptoms[6] at baseline who achieved remission of all B symptoms at any time during treatment)	
N = 35[7]	n = 27 (77%); [95% CI] = [59.9; 89.6]
Quality of life	
No data on quality of life were collected in study SG035-0003.	
Side effects[8]	
AE	
N = 102	n = 100 (9 %)
SAE	
N = 102	n = 25 (25%)
AE of CTCAE grade ≥ 3 (3 – 5)	
N = 102	n = 56 (55%)
Termination of treatment due to AE	
N = 102	n = 20 (20%)
Frequent AE/AE of particular interest	
Peripheral neuropathy (standardized MedDRA query "peripheral neuropathy")	
N = 102	n = 56 (55%)

[4] Number of patients with disease progression/death
[5] Number of patients with disease progression or termination of treatment
[6] Fever, night sweats, weight loss > 10%
[7] Patient with B symptoms at baseline
[8] Assessment based on safety population

Brentuximab vedotin Study SG035-0003	
Peripheral neuropathy (MedDRA preferred term; CTCAE grade 1 – 3[9,10])	
N = 102	Peripheral sensory neuropathy n = 48 (47%) Termination of treatment due to peripheral sensory neuropathy: n = 6 (6%)
	Peripheral motor neuropathy n = 12 (12%) Termination of treatment due to peripheral motor neuropathy: n = 3 (3%)
Fatigue	
N = 102	all CTCAE grades n = 47 (46%) CTCAE grades 3 – 4 n = 2 (2%)
Nausea	
N = 102	all CTCAE grades n = 43 (42%)
Infections of the upper respiratory tract	
N = 102	all CTCAE grades n = 38 (37%)
Diarrhoea	
N = 102	all CTCAE grades n = 37 (36%)
Fever	
N = 102	all CTCAE grades n = 30 (30%) CTCAE grades ≥ 3 n = 2 (2%)
Neutropenia	
N = 102	alle CTCAE grades n = 22 (22%) CTCAE grades 3 – 4 n = 20 (20%)[5]
Vomiting	
N = 102	all CTCAE grades n = 22 (22%)
Cough	
N = 102	all CTCAE grades n = 21 (21%)
Arthralgia	
N = 102	all CTCAE grades n = 19 (19%)
Headache	
N = 102	all CTCAE grades n = 19 (19%)
Abdominal pain	
N = 102	all CTCAE grades n = 17 (17 %) CTCAE grades 3 – 4 n = 2 (2%)
Myalgia	
N = 102	all CTCAE grades n = 17 (17 %)
Constipation	
N = 102	all CTCAE grades n = 16 (16 %)
Pruritus	
N = 102	all CTCAE grades n = 16 (16 %)
Backache	
N = 102	all CTCAE grades n = 14 (14 %)
Sleep disturbance (insomnia)	
N = 102	all CTCAE grades n = 14 (14 %)
Rash	
N = 102	all CTCAE grades n = 14 (14 %)
Alopecia	

[9] Information on CTCAE grades and termination of study participation due to peripheral motor neuropathy taken from the study report on study SG035-0003

[10] No peripheral neuropathy of CTCAE grade > 3 was observed in study SG035-0003

Brentuximab vedotin Study SG035-0003	
N = 102	all CTCAE grades n = 13 (13 %)
Chills	
N = 102	all CTCAE grades n = 13 (13 %)
Dyspnea	
N = 102	all CTCAE grades n = 13 (13 %)
Night sweats	
N = 102	all CTCAE grades n = 12 (12 %)
Anxiety	
N = 102	all CTCAE grades n = 11 (11 %) CTCAE grades ≥ 3 n = 2 (2%)
Lymphadenopathy	
N = 102	all CTCAE grades n = 11 (11 %)
Oropharyngeal pain	
N = 102	all CTCAE grades n = 11 (11 %)
Vertigo	
N = 102	all CTCAE grades n = 11 (11 %)
Decrease in appetite	
N = 102	all CTCAE grades n = 11 (11 %)
Pain in the extremities	
N = 102	all CTCAE grades n = 10 (10 %)

Abbreviations used: CTCAE = common terminology criteria for adverse events; CI = common terminology criteria for adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with an incident; n.a. = not assessable; N = number of patients evaluated; (S)AE = (serious) adverse event

b) Treatment of relapsed or refractory CD30+ Hodgkin lymphoma following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option (ASCT-naive patients):

Not quantifiable

Study results according to endpoints[11]:

Brentuximab vedotin Aggregate case series of ASCT-naive patients[11]	
Mortality	
Overall survival	
No analysis of overall survival is available for the aggregate case series of ASCT-naive patients.	
Morbidity	
Objective response rate (percentage of patients who achieve complete or partial remission within observation period)	
N = 41[12]	n = 22 (54%); [95% CI] = n/a
Complete remission (percentage of patients with complete remission within observation period) N = 41[12]	
	n = 9 (22%); [95% CI] = n/a
Percentage of patients who received a stem-cell transplant following treatment with brentuximab vedotin (Percentage of patients who received a stem-cell transplant after completing treatment with brentuximab vedotin)	
N = 41[12]	n = 8 (19%); [95% CI] = n/a
Quality of life	

[11] Aggregate case series from studies SG035-0001, SG035-0002, SG035-007, and TB-BC010088, as well as 2 case series from named patient programs; details from the G-BA benefit assessment of 1 March 2013 and the dossier submitted by the pharmaceutical company of 31 October 2012

[12] Number of patients in the aggregate case series who received a regulatory-compliant dosage (1.8 mg/kg body weight)

Brentuximab vedotin Aggregate case series of ASCT-naive patients[11]	
No data on quality of life is available.	
Side effects	
AE[13,14]	
N = 59	Not evaluated
SAE	
N = 59	n = 15 (25 %)
AE of CTCAE grade ≥ 3 (3 – 5) N = 59	
	n = 25 (42 %)
Termination of treatment due to AE	
N = 59	n = 7 (12 %)
Frequent AE/AE of particular interest	
Peripheral neuropathy (standardized MedDRA query "peripheral neuropathy")	
N = 59	n = 25 (42 %)

Abbreviations used: ASCT = autologous stem cell transplantation; CTCAE = common terminology criteria for adverse events; n/a = not available; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with an incident; N = number of patients evaluated; (S)AE = (serious) adverse events

c) Treatment of relapsed/refractory systemic anaplastic large cell lymphoma:

Not quantifiable

Study results according to endpoints[15]:

Brentuximab vedotin Study SG035-0004	
Mortality	
Overall survival[16]	
N = 58	Number of patient deaths, n = 19 (33 %); Median overall survival[17] [95% CI] = not achieved [n.a.] Estimated overall survival rate after 12 months [95% CI] = 70% [59; 82]
Morbidity	
Progression-free survival[16] (time from start of treatment until initial documentation of objective tumour progression or death	
N = 58	n[18] = 32 (55 %); Median[17] [95% CI] = 14.3 months [6.9; n.a.]
Incident-free survival[16] (time from start of study treatment until each treatment failure, including disease progression or interruption of treatment for any reason, e.g. toxicity, patient preference, initiation of a new treatment other than stem-cell transplant without documented progression or death)	
N = 58	n[19] = 44 (76 %); Median[17] [95% CI] = 6.7 weeks [4.2; 9.5]
Objective response rate[16] (percentage of patients who achieved complete or partial remission within observation period)	
N = 58	n = 50 (86 %); [95% CI] = [74.6; 93.9]

[13] No descriptive information on the most frequent AEs is available; it is not apparent how many of the patients selected in total from the aggregate case series experienced AEs

[14] All patients identified as ASCT-naive from the aggregate case series were considered, regardless of whether they received brentuximab vedotin in the dosage authorized or not

[15] Data from the SG035-0004 study from the G-BA benefit assessment of 1 March 2013 and from the dossier submitted by the pharmaceutical company

[16] Intention to treat (ITT) assessment

[17] Median overall survival/progression-free or incident-free survival (in months) were estimated using the Kaplan-Meier method

[18] Number of patients with disease progression/death

[19] Number of patients with disease progression or termination of treatment

Brentuximab vedotin Study SG035-0004	
Complete remission[16] (percentage of patients with complete remission within observation period)	
N = 58	n = 34 (58 %);[20]; [95% CI] = [44.9; 71.4]
B symptoms remission rate[16] (percentage of patients with lymphoma-associated B symptoms[21] at baseline who achieved remission of all B symptoms at any time during treatment)	
N = 17[22]	n = 14 (82 %); [95% CI] = [56.6; 96.2]
Quality of life	
No data on quality of life were collected in study SG035-0004.	
Side effects[23]	
AE	
N = 58	n = 58 (100 %)
SAE	
N = 58	n = 24 (41 %)
AE of CTCAE grade ≥ 3 (3 – 5) N = 58	
	n = 36 (62 %) CTCAE grade 3 = 21 (36 %) CTCAE grade 4 = 9 (16 %) CTCAE gradd 5 = 6 (10 %)
Termination of treatment due to AE	
N = 58	n = 16 (28 %)
Frequent AE/AE of particular interest (MedDRA preferred term)	
Peripheral neuropathy (standardized MedDRA query "peripheral neuropathy")	
N = 58	n = 33 (57 %)
Peripheral neuropathy (CTCAE grades 1 – 3[24])	
N = 58	Peripheral sensory neuropathy, n = 24 (41 %), Termination of treatment due to peripheral sensory neuropathy, n = 6 (10 %)[25]
	Peripheral motor neuropathy n = 3 (5 %) Termination of treatment due to peripheral motor neuropathy: n = n/a
Nausea	
N = 58	all CTCAE grades n = 23 (40 %)
Fatigue	
N = 58	all CTCAE grades n = 22 (38 %) CTCAE grades ≥ 3 n = 3 (5 %)
Fever	
N = 58	all CTCAE grades n = 20 (34 %)
Diarrhoea	
N = 58	all CTCAE grades n = 17 (29 %) CTCAE grades ≥ 3 n = 2 (3 %)
Rash	
N = 58	all CTCAE grades n = 14 (24 %)
Constipation	
N = 58	all CTCAE grades n = 13 (22 %)
Neutropenia	

[20] Of the 34 patients with complete remission, 13 had died or progressed at the point of evaluation (p. 86, module 4 B, dossier submitted by the pharmaceutical company)

[21] Fever, night sweats, weight loss > 10%

[22] Patient with B symptoms at baseline

[23] Based on safety population

[24] No peripheral neuropathy of CTCAE grade > 3 was observed in study SG035-0004

[25] Information on termination of study participation due to peripheral sensory neuropathy taken from the study report on study SG035-0004

Brentuximab vedotin Study SG035-0004	
N = 58	all CTCAE grades n = 12 (21 %) CTCAE grades ≥ 3 n = 12 (21 %)
Thrombocytopenia	
N = 58	all CTCAE grades n = 8 (14 %) CTCAE grades ≥ 3 n = 8 (14 %)
Dyspnea	
N = 58	all CTCAE grades n = 11 (19 %)
Infections of the upper respiratory tract	
N = 58	all CTCAE grades n = 11 (19%)
Headache	
N = 58	all CTCAE grades n = 11 (19 %)
Pruritus	
N = 58	all CTCAE grades n = 11 (19 %)
Vomiting	
N = 58	all CTCAE grades n = 10 (17 %) CTCAE grades ≥ 3 n = 2 (3 %)
Cough	
N = 58	all CTCAE grades n = 10 (17 %)
Sleep disturbance (insomnia)	
N = 58	all CTCAE grades n = 9 (16 %)
Myalgia	
N = 58	all CTCAE grades n = 9 (16 %)
Vertigo	
N = 58	all CTCAE grades n = 9 (16 %)
Decrease in appetite	
N = 58	all CTCAE grades n = 9 (16 %)
Alopecia	
N = 58	all CTCAE grades n = 8 (14 %)
Weight loss	
N = 58	all CTCAE grades n = 8 (14 %)
Chills	
N = 58	all CTCAE grades n = 8 (14 %)
Muscle spasms	
N = 58	all CTCAE grades n = 8 (14 %)
Peripheral oedema	
N = 58	all CTCAE grades n = 8 (14 %)
Pain in the extremities	
N = 58	all CTCAE grades n = 8 (14 %) CTCAE grades ≥ 3 n = 2 (3 %)
Anaemia	
N = 58	all CTCAE grades n = 6 (10 %)
Dry skin	
N = 58	all CTCAE grades n = 6 (10 %)
Lymphadenopathy	
N = 58	all CTCAE grades n = 6 (10 %)
Pain	
N = 58	all CTCAE grades n = 6 (10 %)

Abbreviations used: CTCAE = common terminology criteria for adverse events; n/a = not available; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients with an incident; n.a. = not assessable; N = number of patients with data on the relevant endpoint; (S)AE = (serious) adverse events

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

a) and b) treatment of relapsed/refractory CD30+ Hodgkin lymphoma

Target population: approx. 60 – 260 patients

c) Treatment of relapsed/refractory systemic anaplastic large cell lymphoma:

Target population: approx. 15 – 160 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 Adcetris® (active ingredient: brentuximab vedotin) at the following public link (last accessed: 8 April 2013):

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/ 002455/ WC500135055.pdf

Initiation and monitoring of treatment with brentuximab vedotin must be conducted by a specialist for internal medicine, haematology, and oncology experienced in the treatment of this disease.

4. Costs of treatment

Duration of treatment:

Description of therapy	Mode of treatment	Number of treatments (cycles) per patient per year	Treatment days per cycle	Number of treatment days per patient per year
Brentuximab vedotin	Every 3 weeks, intravenous infusion for 30 minutes	8 – 16	1	8 – 16

Consumption:

Description of therapy	Strength (mg)	Number/amount per pack (vial)	Average annual consumption (vials)
Brentuximab vedotin	50	1	24 – 48[26]

Costs:

Cost of pharmaceutical:

Description of therapy	Cost (pharmacy retail price)	Cost after legally mandated rebates
Brentuximab vedotin	€4,920.71	€4,283.78 [€2.05[27]; €634.88[28]]

("Lauer-Taxe", effective 1 April 2013)

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

None

Annual treatment costs:

Description of therapy	Annual treatment costs per patient
Brentuximab vedotin	€102,810.72 – €205,621.44

II.

This resolution takes effect on the day of its publication in the internet on the website of the Federal Joint Committee on 16 May 2013.

[26] Reference: 75.6 kg body weight (microcensus 2009)
[27] Rebate in accordance with SGB V, section 130
[28] Rebate in accordance with SGB V, section 130a

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

Berlin, 16 May 2013

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

The Chair
Hecken