Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee 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: Systemic Anaplastic Large Cell Lymphoma (sALCL))

of 3 December 2020

The Federal Joint Committee (G-BA) resolved to amend the 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 September 2020:

Brentuximab vedotin

Resolution of: 3 December 2020
Entry into force on: 3 December 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 12 May 2020):

Adcetris in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL).

Therapeutic indication of the resolution (resolution of 3 December 2020):

See therapeutic indication according to marketing authorisation

1. Extent of the additional benefit and significance of the evidence

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. In accordance with 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) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. 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 systemic anaplastic large cell lymphoma (sALCL)

Extent of the additional benefit and the significance of the evidence for brentuximab vedotin:

Hint for a minor additional benefit

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↑	Advantage in overall survival
Morbidity	↑	Advantage in the endpoint event-free survival (EFS)
Health-related quality of life	↔	No statistically significant or relevant difference
Side effects	↔	No statistically significant or relevant difference

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

Study results according to endpoints:[1]

ECHELON-2 study:

- Brentuximab vedotin (A) + cyclophosphamide + doxorubicin + prednisone (CHP) vs cyclophosphamide + doxorubicin + vincristine + prednisone (CHOP)
- Double-blind, randomised, placebo-controlled Phase III study in parallel group design (1:1)
- Relevant sub-population: Patients with sALCL;
- Data cut-off: 25 September 2019 and 15 August 2018 (patient-reported endpoints of morbidity and quality of life as well as for the endpoint category side effects)

Mortality

Endpoint	Brentuximab vedotin + CHP		CHOP		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value
Overall survival (data cut-off of 25 September 2019)					
	162	n.a. [n.a.; n.a.] 34 (21)	154	n.a. [n.a.; n.a.] 44 (29)	0.63 [0.40; 0.99] 0.0433

[1] Data from the dossier assessment by the G-BA (published on 15 September 2020) unless otherwise indicated.

Morbidity

Endpoint	Brentuximab vedotin + CHP		CHOP		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Hazard Ratio [95% CI] p value
Progression-free survival (PFS) (presented additionally) [a] (Data cut-off: 25 September 2019)					
	162	n.a. [55.66; -] 51 (31)	154	54.18 [13.44; -] 76 (49)	0.54 [0.38; 0.77] 0.0005
Event-free survival (Data cut-off of 25 September 2019)					
Data cut-off: 25 September 2019	162	55.7 [27.2; n.a.] 70 (43)	154	12.2 [7.2; 32.0] 91 (59)	0.59 [0.43; 0.81] 0.0010
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value
Complete remission (CR) (presented additionally) (Data cut-off: 25 September 2019)					
	162	115 (71)	154	82 (53)	1.36 [1.14; 1.61] 0.0004
Complete remission in patients with B symptomatology at the start of treatment (Data cut-off: 25 September 2019)					
	44 [b]	31 (70)	54 [b]	29 (54)	1.29 [0.94; 1.76] 0.1202
	N	LS MV [SE]	N	LS MV [SE]	MD [c] [95% CI] p value
EQ-5D VAS (change at EoT compared with start of treatment) [d] (Data cut-off: 15 August 2018)					
	149 [e]	8.5 [15.2]	145 [e]	9.0 [15.3]	−0.46 [−3.95; 3.03] 0.7942

(Continuation)

Endpoint	Brentuximab vedotin + CHP		CHOP		Intervention vs control
	N	MV (SD)	N	MV (SD)	MD [95% CI] p value
EORTC QLQ-C30 – Symptom scales (change from start of treatment to EoT) [f] (Data cut-off: 15 August 2018)					
Fatigue	153 [e]	−7.9 (18.26)	146 [e]	−10.0 (18.40)	2.13 [−2.03; 6.29] 0.3153
Pain	153 [e]	−17.8 (18.28)	146 [e]	−22.0 (18.44)	4.21 [0.04; 8.37] 0.0480 Hedges' g: 0.23 [0.00; 0.46]
Nausea and vomiting	153 [e]	−0.2 (8.88)	146 [e]	−3.0 (8.96)	2.77 [0.74; 4.79] 0.0076 Hedges' g: 0.31 [0.08; 0.54]
Dyspnoea	151 [e]	−3.0 (16.73)	146 [e]	−4.1 (16.91)	1.11 [−2.72; 4.94] 0.5702
Loss of appetite	153 [e]	−9.0 (19.06)	146 [e]	−12.0 (19.23)	3.03 [−1.33; 7.38] 0.1729
Insomnia	152 [e]	−17.4 (21.83)	146 [e]	−16.6 (22.04)	−0.84 [−5.83; 4.16] 0.7425
Constipation	153 [e]	−6.7 (16.14)	144 [e]	−8.6 (16.26)	1.91 [−1.78; 5.61] 0.3101
Diarrhoea	153 [e]	1.1 (12.64)	145 [e]	−2.5 (12.73)	3.64 [0.75; 6.53] 0.0134 Hedges' g: 0.29 [0.06; 0.51]
	N	LS MV [SE]	N	LS MV [SE]	MD [c] [95% CI] p value
FACT/GOG-Ntx (change at EoT compared with start of treatment) [g] (Data cut-off: 15 August 2018)					
	152 [e]	−2.1 [4.7]	146 [e]	−0.9 [4.7]	−0.89 [−1.96; 0.18] 0.1021

Health-related quality of life

Endpoint	Brentuximab vedotin + CHP		CHOP		Intervention vs control
	N	MV (SD)	N	MV (SD)	MD [95% CI] p value
EORTC QLQ-C30 – Functional scales (change from start of treatment to EoT) [h] (Data cut-off: 15 August 2018)					
General health status/quality of life	153 [e]	10.6 (16.03)	144 [e]	11.6 (16.15)	−0.94 [−4.61; 2.72] 0.6143
Physical functioning	152 [e]	4.9 (15.96)	146 [e]	4.1 (16.07)	0.79 [−2.86; 4.43] 0.6719
Role functioning	152 [e]	6.9 (21.54)	145 [e]	10.6 (21.72)	−3.66 [−8.59; 1.27] 0.1454
Emotional functioning	153 [e]	9.7 (14.24)	145 [e]	11.1 (14.37)	−1.44 [−4.70; 1.82] 0.3871
Cognitive functioning	153 [e]	2.3 (14.37)	145 [e]	4.3 (14.49)	−2.06 [−5.34; 1.23] 0.2196
Social functioning	153 [e]	5.9 (20.82)	145 [e]	9.6 (20.98)	−3.71 [−8.47; 1.04] 0.1260

Side effects (Data cut-off: 15 August 2018)

Endpoint	Brentuximab vedotin + CHP		CHOP		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value
Adverse events in total					
	160 [i]	159 (99)	154 [i]	150 (97)	
Serious adverse events (SAE)					
	160 [i]	52 (33)	154 [i]	57 (37)	0.87 [0.65; 1.15] 0.3206
AE of NCI-CTCAE grade ≥ 3					
	160 [i]	94 (59)	154 [i]	98 (64)	0.93 [0.78; 1.10] 0.3832

(Continuation)

Therapy discontinuation because of adverse events					
	160 [i]	6 (4)	154 [i]	14 (9)	0.40 [0.15; 1.05] 0.0500
AE of special interest (any degree of severity)					
AE of the SMQ peripheral neuropathy Grade ≤ 2 Grade ≥ 3 SAE	160 [i]	 87(54) 82 (52) 5 (3) 1 (< 1)	154 [i]	 88 (57) 80 (52) 8 (5) 3 (2)	 0.95 [0.78; 1.16]; 0.6352 0.99 [0.80; 1.23]; 0.9213 0.59 [0.19; 1.83]; 0.3530 0.30 [0.03; 3.49]; 0.3037

[a] Data from the dossier on brentuximab vedotin Module 4F of 8 June 2020
[b] Patients with B symptomatology at the start of treatment
[c] Based on an MMRM analysis
[d] Scale: 0–100. Higher values of the scales reflect a better health status.
[e] Number of patients in the evaluation
[f] Scale: 0–100. Higher values on the symptom scales or the individual symptom items reflect more severe symptomatology
[g] Scale 0–44. Higher values reflect fewer symptoms
[h] Scale: 0–100. Higher values of the scales reflect a better health quality of life
[i] Safety population (compliant with marketing authorisation)
Abbreviations used:
CHP = cyclophosphamide + doxorubicin + prednisone; CHOP = cyclophosphamide + doxorubicin + vincristine + prednisone; CTCAE = Common Terminology Criteria for Adverse Events; EoT = end of treatment; CI = confidence interval; LS MV = least squares mean value; MV = mean value; MD = mean difference; N = number of patients evaluated; n = number of patients with (at least one) event; n.a. = not achieved; SD = standard deviation; SE = standard error; vs = versus

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

approx. 125–127 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: 8 September 2020):

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

Treatment with brentuximab vedotin should be initiated and monitored only by specialists in internal medicine, haematology, and oncology experienced in the treatment of patients with peripheral T-cell lymphoma, especially sALCL.

This medicinal product received a conditional marketing authorisation. The EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

There is no data available for patients with sALCL ALK+ with IPI status < 2 because these patients were not included in the ECHELON-2 study.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Brentuximab vedotin	€ 56,668.86 – 75,558.48
Cyclophosphamide	€ 181.73 – € 272.27
Doxorubicin	€ 1,612.08 – 2,149.44
Prednisone	€ 79.44 – 118.70
Total:	€ 58,542.11 – 78,098.89
Additionally required SHI services	€ 5,214.54 – 6,952.72

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 November 2020

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	€ 81	1	6–8	€ 486 – € 648
Cyclophosphamide	Surcharge for the preparation of a solution containing cytostatic agents	€ 81	1	6–8	€ 486 – € 648
Doxorubicin	Surcharge for the preparation of a solution containing cytostatic agents	€ 81	1	6–8	€ 486 – € 648

II. Entry into force

1. **The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 3 December 2020.**
2. **The period of validity of the resolution is limited to 1 July 2021.**

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

Berlin, 3 December 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken