Gemeinsamer Bundesausschuss

# Resolution

## of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Brentuximab Vedotin (reassessment after the deadline: systemic anaplastic large cell lymphoma; first-line; combination with Cyclophosphamide, Doxorubicin, and Prednisone)

of 16 December 2021

At its session on 16 December 2021, 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 amended by the publication of the resolution of D. month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

**I. Annex XII is amended as follows:**

1. The information on brentuximab vedotin in the version of the resolution of 3 December 2020 (Federal Gazette, BAnz AT 04.02.2021 B3) is repealed.
2. 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 2019:

**Brentuximab Vedotin**

Resolution of: 16 December 2021
Entry into force on: 16 December 2021
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 16 December 2021):**

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 under Regulation (EC) No. 141/2000 of the European Parliament and of 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).

<u>Adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL)</u>

**Extent of additional benefit and significance of the evidence of Brentuximab Vedotin in combination with Cyclophosphamide, Doxorubicin and Prednisone (CHP):**

Hint for a minor additional benefit

**Study results according to endpoints:**[1]

Adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL)

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ risk of bias | Summary |
|---|---|---|
| Mortality | ↔ | No relevant difference for the benefit assessment |
| Morbidity | ↑ | Advantage in the endpoint of event-free survival (EFS) |
| Health-related quality of life | ↔ | No relevant difference for the benefit assessment |
| Side effects | ↔ | No relevant difference for the benefit assessment |
| Explanations:<br>↑: statistically significant and relevant positive effect with low/unclear reliability of data<br>↓: statistically significant and relevant negative effect with low/unclear reliability of data<br>↑↑: statistically significant and relevant positive effect with high reliability of data<br>↓↓: statistically significant and relevant negative effect with high reliability of data<br>↔: no statistically significant or relevant difference<br>∅: There are no usable data for the benefit assessment.<br>n.a.: not assessable | | |

ECHELON-2 study:

- brentuximab vedotin (A) + cyclophosphamide + doxorubicin + prednisone (CHP) versus 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-offs: 05.11.2020; 15.08.2018

[1] Data from the dossier assessment of the G-BA (published on 1. Oktober 2021), and from the amendment of the G-BA to the dossier assessment (published on 16 December 2021), unless otherwise indicated.

**Mortality**

| **Endpoint** | **Brentuximab Vedotin (A) + CHP** | | **CHOP** | | A+CHP vs CHOP |
|---|---|---|---|---|---|
| | 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 [95% CI] p-value Absolute difference (AD)[a] |
| **Overall survival** (data cut-off of 05.11.2020) | | | | | |
| Stratified analysis | 162 | n.a. [n.a.; n.a.] *39 (24)* | 154 | n.a. [n.a.; n.a.] *49 (32)* | 0.66 [0.43; 1.01] 0.053[b] |

**Morbidity**

| **Endpoint** | **Brentuximab Vedotin (A)+ CHP** | | **CHOP** | | A+CHP vs CHOP |
|---|---|---|---|---|---|
| | 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 Absolute difference (AD)[a] |
| **Progression-free survival (PFS)**[c] (presented additionally; data cut-off 05.11.2020) | | | | | |
| | 162 | n.a. [55,66; -] *53 (33)* | 154 | 54.18 [13,44; -] *77 (50)* | 0.55 [0.39; 0.79] 0.0009[b] |
| **Event-free survival** (data cut-off of 05.11.2020) | | | | | |
| | 162 | 55.7 [26.2; n.a.] *74 (46)* | 154 | 9.0 [5.5; 32.0] *92 (60)* | 0.63 [0.46; 0.86] 0.0034[b] + 46.7 months |

(continuation)

| **Endpoint** | **Brentuximab Vedotin (A)+ CHP** | | **CHOP** | | A+CHP vs CHOP |
|---|---|---|---|---|---|
| | N | *Patients with event n (%)* | N | *Patients with event n (%)* | Relative risk [95% CI] p-value |
| **Complete remission (CR)** (presented additionally; data cut-off of 15.08.2018) | | | | | |
| | 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 of 15.08.2018) | | | | | |
| | 44[d] | 31 (70) | 54[d] | 29 (54) | 1.29 [0.94; 1.76] 0.1202 |
| **Endpoint** | N | LS-MV [SE] | N | LS-MV [SE] | MD[e] [95% CI] p-value |
| **EQ-5D VAS** (change at the EoT (end of treatment) compared to the start of treatment; data cut-off of 15.08.2018)[f] | | | | | |
| | 149[g] | 8.5 [15.2] | 145[g] | 9.0 [15.3] | -0.46 [-3.95; 3.03] 0.7942 |
| **Endpoint** | N | MV (SD) | N | MV (SD) | MD[e] [95% CI] p-value |
| **EORTC QLQ-C30 - symptom scales** (change at the end of treatment compared to the start of treatment; data cut-off of 15.08.2018)[h] | | | | | |
| Fatigue | 153[g] | -7.9 (18.26) | 146[g] | -10.0 (18.40) | 2.13 [-2.03; 6.29] 0.3153 |
| Pain | 153[g] | -17.8 (18.28) | 146[g] | -22.0 (18.44) | 4.21 [0.04; 8.37] 0.0480 Hedges' g: 0.23 [0.00; 0.46] |

(continuation)

| **Endpoint** | **Brentuximab Vedotin (A)+ CHP** | | **CHOP** | | A+CHP vs CHOP |
|---|---|---|---|---|---|
| | N | MV (SD) | N | MV (SD) | MD[e] [95% CI] p-value |
| Nausea and vomiting | 153[g] | -0.2 (8.88) | 146[g] | -3.0 (8.96) | 2.77 [0.74; 4.79] 0.0076 Hedges' g: 0.31 [0.08; 0.54] |
| Dyspnoea | 151[g] | -3.0 (16.73) | 146[g] | -4.1 (16.91) | 1.11 [-2.72; 4.94] 0.5702 |
| Appetite loss | 153[g] | -9.0 (19.06) | 146[g] | -12.0 (19.23) | 3.03 [-1.33; 7.38] 0.1729 |
| Insomnia | 152[g] | -17.4 (21.83) | 146[g] | -16.6 (22.04) | -0.84 [-5.83; 4.16] 0.7425 |
| Constipation | 153[g] | -6.7 (16.14) | 144[g] | -8.6 (16.26) | 1.91 [-1.78; 5.61] 0.3101 |
| Diarrhoea | 153[g] | 1.1 (12.64) | 145[g] | -2.5 (12.73) | 3.64 [0.75; 6.53] 0.0134 Hedges' g: 0.29 [0.06; 0.51] |
| **Endpoint** | N | LS-MV [SE] | N | LS-MV [SE] | MD[e] [95% CI] p-value |
| **FACT/GOG-Ntx** (change at the end of treatment compared to the start of treatment, data cut-off of 15.08.2018)[i] | | | | | |
| | 152[g] | -2.1 [4.7] | 146[g] | -0.9 [4.7] | -0.89 [-1.96; 0.18] 0.1021 |

**Health-related quality of life**

| Endpoint | Brentuximab Vedotin (A)+ CHP | | CHOP | | A+CHP vs CHOP |
|---|---|---|---|---|---|
| | N | MV (SD) | N | MV (SD) | MD[e] [95% CI] p-value |
| **EORTC QLQ-C30 - functional scales** (change at the end of treatment compared to the start of treatment; data cut-off of 15.08.2018)[j] | | | | | |
| General health status/quality of life | 153[g] | 10.6 (16.03) | 144[g] | 11.6 (16.15) | -0.94 [-4.61; 2.72] 0.6143 |
| Physical functioning | 152[g] | 4.9 (15.96) | 146[g] | 4.1 (16.07) | 0.79 [-2.86; 4.43] 0.6719 |
| Role functioning | 152[g] | 6.9 (21.54) | 145[g] | 10.6 (21.72) | -3.66 [-8.59; 1.27] 0.1454 |
| Emotional functioning | 153[g] | 9.7 (14.24) | 145[g] | 11.1 (14.37) | -1.44 [-4.70; 1.82] 0.3871 |
| Cognitive functioning | 153[g] | 2.3 (14.37) | 145[g] | 4.3 (14.49) | -2.06 [-5.34; 1.23] 0.2196 |
| Social functioning | 153[g] | 5.9 (20.82) | 145[g] | 9.6 (20.98) | -3.71 [-8.47; 1.04] 0.1260 |

**Side effects (data cut-off of 15.08.2018)**

| Endpoint | Brentuximab vedotin (A)+ CHP | | CHOP | | A+CHP vs CHOP |
|---|---|---|---|---|---|
| | N | *Patients with event n (%)* | N | *Patients with event n (%)* | Relative risk [95% CI] p-value[k] |
| **Total adverse events (presented additionally)** | | | | | |
| | 160[l] | 159 (99) | 154[l] | 150 (97) | - |

| Endpoint | Brentuximab vedotin (A)+ CHP | | CHOP | | A+CHP vs CHOP |
|---|---|---|---|---|---|
| | N | *Patients with event n (%)* | N | *Patients with event n (%)* | Relative risk [95% CI] p-value[k] |
| **Serious adverse events (SAE)** | | | | | |
| | 160[l] | 52 (33) | 154[l] | 57 (37) | 0.87 [0.65; 1.15] 0.3206 |
| **Severe adverse events (CTCAE grade ≥ 3)** | | | | | |
| | 160[l] | 94 (59) | 154[l] | 98 (64) | 0.93 [0.78; 1.10] 0.3832 |
| **AE, which led to the discontinuation of the study medication** | | | | | |
| | 160[l] | 6 (4) | 154[l] | 14 (9) | 0.40 [0.15; 1.05] 0.0500 |
| **AEs of special interest** | | | | | |
| AE of SMQ peripheral neuropathy | | | | | |
| Any severity grade | 160[l] | 87 (54) | 154[l] | 88 (57) | 0.95 [0.78; 1.16] 0.6352 |
| Grade ≤ 2 | 160[l] | 82 (52) | 154[l] | 80 (52) | 0.99 [0.80; 1.23] 0.9213 |
| Grade ≥ 3 | 160[l] | 5 (3) | 154[l] | 8 (5) | 0.59 [0.19; 1.83] 0.3530 |
| SAE | 160[l] | 1 (< 1) | 154[l] | 3 (2) | 0.30 [0.03; 3.49] 0.3037 |

a Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
b Hazard ratio and 95% CI based on Cox regression model. p-value based on stratified log-rank test with factors ALK+ (yes/no) and IPI score (0-1/2-3/4-5)
c Data from the dossier for the brentuximab vedotin module 4F (dated 21.06.2021)
d Patients with B symptomatology at the start of treatment
e Based on MMRM analyses
f Scale: 0–100. Higher scores on the scales mean better health status.
g Number of patients evaluated
h Scale: 0–100. Higher scores on the symptom scales or the individual symptom items mean more severe symptomatology.
i Scale 0–44. Higher scores mean fewer disorders.
j Scale: 0–100. Higher scores on the scales mean a better quality of life.
k p-value based on Cochran-Mantel-Haenszel Chi-square test, stratified by ALK+ (yes/no) and IPI score (0-1/2-3/4-5)
l Safety population compliant with the marketing authorisation

Abbreviations used:
AD = absolute difference; A + CHP = brentuximab vedotin + cyclophosphamide + doxorubicin + prednisone; CHOP = cyclophosphamide + doxorubicin + vincristine + prednisone; CR = complete remission; CTCAE = Common Terminology Criteria for Adverse Events; EORTC-QLQ-C30 = European Organisation for Research and

Treatment of Cancer Quality of Life Questionnaire C30; EoT = end of treatment; EQ-5D-VAS = Visual Analogue Scale of the EuroQol-5 Dimension Questionnaire; FACT/GOG-Ntx = Functional Assessment of Cancer Therapy / Gynaecologic Oncology Group-Neurotoxicity; HR = hazard ratio; 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.c. = not calculable; n.a. = not achieved; PFS = progression-free survival; SD = standard deviation; SE = standard error; vs = versus

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

Adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL)

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: 20 September 2021):

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

Treatment with the active ingredient should only be initiated and monitored by specialists in internal medicine, haematology and oncology, experienced in the treatment of patients with periphery T-cell lymphoma, in particular sALCL.

This medicine received a conditional marketing authorisation. 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.

No data are available for adults with ALK-positive sALCL with IPI status < 2 as these patients were not included in the ECHELON-2 study.

## 4. Treatment costs

**Annual treatment costs:**

Adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL)

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| Medicinal product to be assessed: | |
| Brentuximab vedotin | € 58,224.78 - € 77,633.04 |
| Cyclophosphamide | € 186.92 - € 280.12 |
| Doxorubicin | € 1,657.80 - € 2,210.40 |
| Prednisone | € 81.73 - € 122.15 |
| Total: | € 60,151.23 - € 80,245.71 |
| Additionally required SHI services | € 4,924.92 - € 6,566.56 |

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 December 2021)

Other SHI services:

| 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 production of a solution containing cytostatic agents | € 71 | 1 | 6 – 8 | € 426 - € 568 |
| Doxorubicin | Surcharge for production of a solution containing cytostatic agents | € 71 | 1 | 6 – 8 | € 426 - € 568 |

**II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 December 2021.**

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

Berlin, 16 December 2021

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

Prof. Hecken