Gemeinsamer Bundesausschuss

Resolution

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: Pembrolizumab (New Therapeutic Indication: Hodgkin lymphoma, pretreated patients, ≥ 3 years)

of 16 September 2021

At its session on 16 September 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 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 point 4 to the information on the benefit assessment of pembrolizumab, as amended by the resolution of 14 May 2020, for the indication "...as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 .":**

Pembrolizumab

Resolution of: 16 September 2021
Entry into force on: 16 September 2021
BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 9 March 2021):

KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Therapeutic indication of the resolution (resolution of 16 September 2021):

This is an indication extension for pembrolizumab as monotherapy for the treatment of paediatric patients, as well as an earlier treatment in adults with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

The indication for the treatment of adults in the therapeutic situation after failure of autologous stem cell transplantation (ASCT) and treatment with brentuximab vedotin (BV), or after failure of treatment with BV when ASCT is not an option, is the subject of the resolution on the benefit assessment of pembrolizumab dated 17.11.2017.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

a) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option

Appropriate comparator therapy:

- Therapy according to doctor's instructions

a1) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is the appropriate therapy as determined by doctor's instructions.

Extent and probability of the additional benefit of pembrolizumab compared to a brentuximab vedotin:

Hint of a considerable additional benefit

a2) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is not the appropriate therapy as determined by doctor's instructions.

Extent and likelihood of additional benefit of pembrolizumab compared to all other treatment options in the setting of therapy as determined by doctor's instructions:

An additional benefit is not proven

b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Appropriate comparator therapy:

- Therapy according to doctor's instructions

Extent and probability of the additional benefit of pembrolizumab compared to therapy according to the doctor's instructions:

An additional benefit is not proven

Study results according to endpoints:[1]

a1) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is the appropriate therapy as determined by doctor's instructions.

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	↑	Benefits in the endpoints of exhaustion, pain, and appetite loss
Health-related quality of life	↑	Benefits in the endpoints of global health status, physical, emotional, and social functioning, and role functioning
Side effects	↑	Statistically significant advantage in the endpoint severe AEs, but no difference relevant for the benefit assessment

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

[1] Data from the dossier assessment of the IQWiG (A21-35) and from the addendum (A21-104), unless otherwise indicated.

KEYNOTE 204 study: Pembrolizumab vs brentuximab vedotin

Relevant sub-population: Patients with relapsed or refractory classical Hodgkin lymphoma treated with ≥ 2 prior therapies

Mortality

Endpoint	**Pembrolizumab**		**Brentuximab vedotin**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months[b] [95% CI] *Patients with event n (%)*	Effect estimator HR [95 %- CI][c] p-value[d,e] Absolute difference (AD)[a]
Mortality					
Overall mortality[e]	151	n. d. 16 (10.6)	153	n. d. 27 (17.6)	RR: 0.60 [0.34; 1.07] 0.080[f]

Morbidity

Endpoint	**Pembrolizumab**		**Brentuximab vedotin**		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months[b] [95% CI] *Patients with event n (%)*	Effect estimator HR [95 % CI] [c] p-value[d] Absolute difference (AD)[a]
Symptomatology (EORTC QLQ-C30; time to first deterioration[g])					
Exhaustion	121	n.a. [8.3; n.c.] 49 (40.5)	124	4.1 [2.8; 6.0] 64 (51.6)	0.57 [0.39; 0.83] 0.004
Nausea and vomiting	121	24.8 [10.3; n.c.] 41 (33.9)	124	n.a. [5.8; n.c.] 41 (33.1)	0.72 [0.46; 1.13] 0.155
Pain	121	24.6 [11.8; n.c.] 42 (34.7)	124	5.5 [4.1; 8.7] 56 (45.2)	0.51 [0.33; 0.78] 0.002 AD: +19.1 months
Dyspnoea	121	n.a. [15.1; n.c.] 37 (30.6)	124	12.3 [10.8; n.c.] 37 (29.8)	0.75 [0.47; 1.20] 0.239

Endpoint	Pembrolizumab		Brentuximab vedotin		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months[b] [95% CI] *Patients with event n (%)*	Effect estimator HR [95 % CI][c] p-value[d] Absolute difference (AD)[a]
Insomnia	121	n.a. [8.5; n.c.] 46 (38.0)	124	8.3 [4.9; 17.5] 49 (39.5)	0.75 [0.49; 1.15] 0.190
Appetite loss	121	25.7 [25.7; n.c.] 26 (21.5)	124	11.0 [4.5; n.c.] 45 (36.3)	0.37 [0.22; 0.61] <0.001 AD: +14.7 months
Constipation	121	24.9 [24,9; n. c.] 33 (27.3)	124	27.0 [12.2; 27.0] 31 (25.0)	0.81 [0.48; 1.36] 0.424
Diarrhoea	121	24.6 [11.1; n.c.] 39 (32.2)	124	n.a. [7.5; n.c.] 34 (27.4)	0.91 [0.57; 1.45] 0.689
Health status (EQ-5D VAS)					
≥ 7 points	121	n.a. [15,1; n. c.] 38 (31,4)	124	8.6 [5.6; n.c.] 45 (36.3)	0.69 [0.44; 1.08] 0.105
≥ 10 points	121	n.a. 34 (28.1)	124	11.0 [7.5; n.c.] 43 (34.7)	0.65 [0.41; 1.03] 0.065
B symptoms[i]	84[j]	n.a. 8 (9.5)	93[j]	n.a. 12 (12.9)	0.40 [0.15; 1.06]; 0.067
Fever	84[j]	n. d.	93[j]	n. d.	n. d.
Night sweats	84[j]	n. d.	93[j]	n. d.	n. d.
Weight loss	84[j]	n. d.	93[j]	n. d.	n. d.

Health-related quality of life

Endpoint	Pembrolizumab		Brentuximab vedotin		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months[b] [95% CI] *Patients with event n (%)*	Effect estimator HR [95 % CI][c] p-value[d] Absolute difference (AD)[a]
EORTC QLQ-C30 (time to first deterioration[k])					
Global health status	121	19.5 [11.1; 26.2] 43 (35.5)	124	6.5 [4.4; 11.6] 52 (41.9)	0.57 [0.37; 0.87] 0.009 AD: +13 months
Physical functioning	121	n.a. [12.9; n.c.] 38 (31.4)	124	8.5 [6.2; 19.5] 49 (39.5)	0.52 [0.33; 0.80] 0.003
Role functioning	121	n.a. [8.4; n.n.] 47 (38.8)	124	4.5 [3.0; 8.5] 63 (50.8)	0.51 [0.35; 0.76] <0.001
Emotional functioning	121	25.7 [11.1; n.c.] 41 (33.9)	124	6.4 [4.5; 10.8] 53 (42.7)	0.53 [0.35; 0.82] 0.004 AD: +19.3 months
Cognitive functioning	121	13.1 [5.7; n.c.] 52 (43.0)	124	6.1 [4.2; n.c.] 50 (40.3)	0.83 [0.56; 1.24] 0.375
Social functioning	121	17.0 [11.1; n. c.] 46 (38.0)	124	7.9 [4.2; 11.4] 50 (40.3)	0.54 [0.35; 0.83] 0.005 AD: +9.1 months

Side effects[l]

Endpoint	Pembrolizumab		Brentuximab vedotin		Intervention vs control
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months[b] [95% CI] *Patients with event n (%)*	Effect estimator HR [95 % CI][c] p-value[d] Absolute difference (AD)[a]
Total adverse events (presented additionally)					
	121	0.5 [0.1; 0.7][m] 118 (97.5)	125	0.5 [0.3; 0.7][m] 119 (95.2)	-
Serious adverse events (SAE)					
	121	n.a. [25.9; n.c.][m] 36 (29.8)	125	n.a. [13.7; n.c.][m] 30 (24.0)	0.92 [0.56; 1.51] 0.736
Severe adverse events (CTCAE grade 3 or 4)					
	121	13.4 [9.2; n.c.][m] 55 (45.5)	125	10.5 [5.6; n.c.][m] 55 (44.0)	0.67 [0.46; 0.99] 0.043 AD: + 2.9 months
Therapy discontinuation due to adverse events					
	121	n.a. 16 (13.2)	125	n.a. 21 (16.8)	0.54 [0.28; 1.06] 0.072
Immune-mediated SAEs					
	121	n.a. 11 (9.1)	125	n.a. 5 (4.0)	1.80 [0.62; 5.27] 0.282
Immune-mediated severe AEs (CTCAE grade 3 or 4)					
	121	n.a. 10 (8.3)	125	n.a. 5 (4.0)	1.45 [0.49; 4.32] 0.506

a. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
b. Product-limit (Kaplan-Meier) method
c. Cox-Proportional-Hazards-Model with treatment as a covariate stratified by prior ASCT (yes vs no) and disease status after first-line therapy (primary refractory vs early relapse < 12 months after first-line therapy vs late relapse ≥ 12 months after first-line therapy)
d. Two-sided p-value (Wald test)
e. Evaluations of overall survival were not planned at the 2nd data cut-off; no data available in Module 4 A. For the present benefit assessment, the rate of deaths is used as a substitute. The results are only available for the total population. The results on deaths were taken from the data on study discontinuations.
f. IQWiG calculation, unconditional exact test (CSZ method)
g. defined as an increase in score of at least 10 points compared to baseline

i. Operationalised as the time to the first appearance of at least one B symptom (fever > 38°C, night sweats, unexplained weight loss > 10% of body weight in ≤ 6 months).
j. Only patients who did not show any B symptoms at the start of the study will be considered.
k. defined as a decrease in score of at least 10 points compared to baseline
l. Exclusively the MedDRA terms "neoplasm progression", "malignant neoplasm progression", and "disease progression"
m. IQWiG calculation (weeks*7*12/365.25)

Abbreviations used:
AD: Absolute difference; auto: autologous; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HR: Hazard ratio; CI: confidence interval; n: number of patients with (at least 1) event; N: Number of patients evaluated; n. c.: not calculable; n. a.: not achieved; SAE: serious adverse event; SCT: stem cell transplantation; RCT: randomised controlled trial; RR: relative risk; AE: adverse event; VAS: visual analogue scale; vs = versus

a2) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option and for whom brentuximab vedotin is not the appropriate therapy as determined by doctor's instructions.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	There are no usable data for the benefit assessment.
Morbidity	∅	There are no usable data for the benefit assessment.
Health-related quality of life	∅	There are no usable data for the benefit assessment.
Side effects	∅	There are no usable data for the benefit assessment.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
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b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Summary of results for relevant clinical endpoints

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

(a) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option

approx. 110 to 220 patients

b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

approx. 10 to 20 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 Keytruda (active ingredient: pembrolizumab) at the following publicly accessible link (last access: 26 May 2021):
https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_de.pdf

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, or specialists in paediatrics and adolescent medicine specialising in paediatric haematology and oncology who are experienced in the treatment of patients with classical Hodgkin lymphoma (cHL).

In addition, for the treatment of children and adolescents, the requirements for paediatric oncology must be observed according to the guideline.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient pass. The training material for health professionals and the patient pass contain, in particular, instructions on the management of immune-mediated side effects potentially occurring with KEYTRUDA as well as on infusion-related reactions.
The prescribing doctor must discuss with the patient the risks of therapy with KEYTRUDA. The patient pass should be made available to the patient.

4. Treatment costs

Annual treatment costs:

(a) Adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab	€ 99,706.18
Appropriate comparator therapy:	
Therapy according to doctor's instructions[a]	
Brentuximab vedotin	€ 168,851.86
Vinblastine	€ 5,891.99 - € 11,783.98
Radiotherapy	patient-individual
allogeneic stem cell transplantation	patient-individual

Designation of the therapy	Annual treatment costs/ patient
autologous stem cell transplantation	patient-individual
[a] Costs are only presented for the active ingredients brentuximab vedotin and vinblastine. In addition to these, the medicinal products etoposide, vinorelbine, gemcitabine, bendamustine and lenalidomide also represent suitable comparators for the present benefit assessment in the context of therapy according to the doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore, no costs are presented for these medicinal products.	

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

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	8.7 – 17.4	€ 617.02 - € 1,234.05
Brentuximab vedotin	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 81	1	17.4	€ 1,409.40
Vinblastine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	1	52.1	€ 4,220.10

b) Paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Pembrolizumab	€ 49,853.09 € - 99,706.18
Appropriate comparator therapy:	
Therapy according to doctor's instructions[b]	
[b] All medicinal therapies that represent a suitable comparator for the present benefit assessment in the context of therapy according to the doctor's instructions are not approved in the present therapeutic indication, which is why no costs are presented for these medicinal products	

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

Costs for additionally required SHI services: not applicable

Other SHI services:

Designation of therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 71	1	17.4	€ 1,234.05

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

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

Berlin, 16 September 2021

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

Prof. Hecken