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)
Lisocabtagene maraleucel (new therapeutic indication: Diffuse large B-cell lymphoma, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma and grade 3B follicular lymphoma, after 1 prior therapy, relapse within 12 months or refractory)

of 16 November 2023

At its session on 16 November 2023, 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 by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added to the information on the benefit assessment of Lisocabtagene maraleucel in accordance with the resolution of 6 April 2023 last modified on 1 June 2023:

Lisocabtagene maraleucel

Resolution of: 16 November 2023
Entry into force on: 16 November 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 28 April 2023):

Breyanzi is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy.

Therapeutic indication of the resolution (resolution of 16 November 2023):

See new therapeutic indication according to marketing authorisation.

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

a) Adults with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), who are eligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

Appropriate comparator therapy:

Induction therapy with
- R-GDP (rituximab, gemcitabine, cisplatin, dexamethasone) *or*
- R-ICE (rituximab, ifosfamide, carboplatin, etoposide) *or*
- R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin)

followed by high-dose therapy with autologous or allogeneic stem cell transplantation if there is a response to induction therapy[1]

Extent and probability of the additional benefit of lisocabtagene maraleucel compared with induction therapy with R-GDP, R-ICE or R-DHAP followed by high-dose therapy with autologous stem cell transplantation:

Hint for a considerable additional benefit

[1] Taking into account the requirements of the Guideline for Inpatient Treatment Methods (last revised 18 October 2023): Section 4, paragraph 2, number 4

b1) Adults with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL) and follicular lymphoma grade 3B (FL3B), who are ineligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

Appropriate comparator therapy:

Therapy according to doctor's instructions under consideration of

- polatuzumab in combination with bendamustine and rituximab *and*
- tafasitamab in combination with lenalidomide

Extent and probability of the additional benefit of lisocabtagene maraleucel compared to the appropriate comparator therapy:

An additional benefit is not proven.

b2) Adults with primary mediastinal large B-cell lymphoma (PMBCL) who are ineligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

Appropriate comparator therapy:

- Pembrolizumab monotherapy

or

- Nivolumab in combination with brentuximab vedotin

Extent and probability of the additional benefit of lisocabtagene maraleucel compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[2]

a) Adults with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), who are eligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

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 failure of the curative therapeutic approach (event rate and event-free survival)
Health-related quality of life	n.a.	There are no assessable data.
Side effects	↔	No relevant differences for the benefit assessment. Advantages and disadvantages in the specific AEs, in detail.
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 ∅: No data available. n.a.: not assessable		

TRANSFORM study:

- open-label, randomised phase III study
- Lisocabtagene maraleucel versus induction therapy with R-GDP, R-ICE or R-DHAP followed by high-dose therapy (HDT) with autologous stem cell transplantation (autoSCT)
- 4th data cut-off from 13 May 2022 (primary analysis)

[2] Data from the dossier assessment of the IQWiG (A23-48) and from the addendum (A23-98), unless otherwise indicated.

Mortality

Endpoint	**Lisocabtagene maraleucel**		**Induction therapy + HDT + autoSCT**		Intervention vs control
	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[a]
Overall survival					
DLBCL, HGBCL, PMBCL, FL3B	92[b]	n.r. [29.5; n.c.] 28 (30.4)	92[b]	29.9 [17.9; n.c.] 38 (41.3)	0.72 [0.44; 1.18] 0.197
DLBCL[c]	60	n.r. [29.54; n.c.] 14 (23.3)	58	n.r. [17.01; n.c.] 24 (41.4)	0.49 [0.26; 0.96] 0.036
HGBCL[c]	22	13.31 [7.85; n.c.] 13 (59.1)	21	16.26 [5.29; n.c.] 12 (57.1)	0.93 [0.42; 2.05] 0.857
PMBCL[c]	8	n.r. [11.04; n.c.] 1 (12.5)	9	n.r. [17.87; n.c.] 1 (11.1)	1.30 [0.08; 20.92] 0.854
FL3B[d]	1	-	0	-	-
Effect modification for the endpoint of overall survival for the age characteristic (interaction: 0.007[e])					
< 65 years	56	n.r. 9 (16.1)	67	n.r. [17.9; n.c.] 27 (40.3)	0.32 [0.15; 0.68] 0.003[f]
≥ 65 years	36	23.0 [12.0; n.c.] 19 (52.8)	25	29.9 [16.3; n.c.] 11 (44.0)	1.40 [0.66; 2.96] 0.378[f]

Morbidity

Endpoint	**Lisocabtagene maraleucel**		**Induction therapy + HDT + autoSCT**		Intervention vs control
	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[a] Absolute difference (AD)[k]
Progression-free survival (PFS)[g]					
DLBCL, HGBCL, PMBCL, FL3B	92[b]	n.r. [12.55; n.c.] 37 (40.2)	92[b]	6.18 [4.27; 8.57] 52 (56.5)	0.40 [0.26; 0.62] < 0.0001
Failure of the curative therapeutic approach					
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative risk [95% CI] p value[o] Absolute difference (AD)[k]
Event rate[h]					
DLBCL, HGBCL, PMBCL, FL3B	92[b]	50 (54.3)	92[b]	76 (82.6)	0.67 [0.55; 0.82] < 0.001 AD = - 28.3%
Death	92[b]	4 (4.3)	92[b]	2 (2.2)	-
Progress after achieving a CR or PR	92[b]	31 (33.7)	92[b]	47 (51.1)	-
CR or PR not achieved until 9 weeks after randomisation	92[b]	4 (4.3)	92[b]	17 (18.5)	-
CR not achieved by week 18 after randomisation	92[b]	8 (8.7)	92[b]	5 (5.4)	-
Start of subsequent antineoplastic therapy due to efficacy concerns	92[b]	3 (3.3)	92[b]	5 (5.4)	-

(continuation)

Endpoint	Lisocabtagene maraleucel		Induction therapy + HDT + autoSCT		Intervention vs control
	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*	Hazard ratio [95% CI] p value[a] Absolute difference (AD)[k]
Event-free survival (EFS)					
DLBCL, HGBCL, PMBCL, FL3B	92[b]	11.7 [6.0; n.c.] 50 (54.3)	92[b]	2.4 [2.2; 4.5] 76 (82.6)	0.37 [0.26; 0.53] < 0.001 AD = + 9.3 months
DLBCL[i]	60	n.r. [6.64; n.c.] 28 (46.7)	58	3.01 [2.17; 5.62] 49 (84.5)	0.33 [0.21; 0.53] < 0.0001
HGBCL[i]	22	4.34 [4.01; 11.70] 19 (86.4)	21	2.17 [0.85; 3.88] 19 (90.5)	0.43 [0.22; 0.82] 0.0103 AD = + 2.17 months
PMBCL[i]	8	n.r. [4.21; n.c.] 3 (37.5)	9	2.17 [0.95; n.c.] 7 (77.8)	0.23 [0.06; 0.93] 0.039
FL3B[d]	1	-	0	-	-
Symptomatology					
EORTC-QLQ-C30					
There are no usable data[j]					
FACT-LymS					
There are no usable data[j]					
Health status (EQ-5D VAS)					
There are no usable data[j]					

Health-related quality of life

EORTC-QLQ-C30
There are no usable data[j]

Side effects

Endpoint	**Lisocabtagene maraleucel**		**Induction therapy + HDT + autoSCT**		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[a] Absolute difference (AD)[k]
Total adverse events (presented additionally)					
DLBCL, HGBCL, PMBCL, FL3B	92[b]	0.10 [0.10; 0.30] 92 (100)	91[b]	0.10 [0.10; 0.10] 90 (98.9)	-
DLBCL[c]	60	0.10 [0.07; 0.26] 60 (100)	58	0.11 [0.07; 0.13] 57 (98.3)	-
HGBCL[c]	22	0.13 [0.07; 0.30] 22 (100)	20	0.07 [0.03; 0.10] 20 (100)	-
PMBCL[c]	8	0.43 [0.03; 0.72] 8 (100)	9	0.13 [0.03; 0.30] 9 (100)	-
FL3B[d]	1	-	0	-	-
Serious adverse events (SAE)					
DLBCL, HGBCL, PMBCL, FL3B	92[b]	4.4 [2.2; n.c.] 44 (47.8)	91[b]	3.1 [2.8; n.c.] 45 (49.5)	0.89 [0.58; 1.36] 0.594
DLBCL[c]	60	4.4 [2.79; n.r.] 24 (40.0)	58	3.65 [2.73; n.r.] 29 (50.0)	0.73 [0.42; 1.26] 0.252
HGBCL[c]	22	1.54 [1.02; 3.52] 17 (77.3)	20	3.02 [1.58; n.r.] 9 (45.0)	2.04 [0.91; 4.60] 0.086
PMBCL[c]	8	n.r. [0.03; n.r.] 2 (25.0)	9	n.r. [0.30; n.r.] 4 (44.4)	0.51 [0.09; 2.79] 0.436
FL3B[d]	1	-	0	-	-

Endpoint	Lisocabtagene maraleucel		Induction therapy + HDT + autoSCT		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 [a] Absolute difference (AD)[k]
Severe adverse events (CTCAE grade ≥ 3)					
DLBCL, HGBCL, PMBCL, FL3B	92[b]	0.60 [0.40; 0.90] 85 (92.4)	91[b]	0.50 [0.40; 0.80] 81 (89.0)	1.17 [0.86, 1.61] 0.322
DLBCL[c]	60	0.54 [0.39; 0.95] 54 (90.0)	58	0.67 [0.36; 1.22] 50 (86.2)	1.17 [0.79; 1.72] 0.437
HGBCL[c]	22	0.61 [0.3; 0.92] 22 (100)	20	0.43 [0.33; 0.85] 19 (95)	1.36 [0.7; 2.65] 0.369
PMBCL[c]	8	1.08 [0.03; 1.91] 7 (87.5)	9	0.33 [0.26; 0.89] 8 (88.9)	0.374 [0.11; 1.27] 0.114
FL3B[d]	1	-	0	-	-
Therapy discontinuation due to adverse events					
DLBCL, HGBCL, PMBCL, FL3B	92[b]	n.r. 0 (0)	91[b]	n.r. 4 (4.4)	n.a. 0.054[p]
Specific adverse events (for total population with DLBCL, HGBCL, PMBCL, FL3B)					
Cytokine release syndrome (CRS; PT)[q]					
	92[b]	n.r. [1.48; n.c.] 45 (48.9)	91[b]	n.r. 0 (0)	n.a. < 0.001[p]
Serious CRS[l,r]	92[b]	n.r. 12 (13.0)	91[b]	n.r. 0 (0)	n.a. < 0.001[p]
Neurological toxicity (SOC nervous system disorders)					
	92[b]	1.4 [1.2; n.c.] 54 (58.7)	91[b]	3.3 [2.8; n.c.] 44 (48.4)	1.36 [0.90; 2.06] 0.141
Severe neurological toxicity[m]	92[b]	n.r. 10 (10.9)	91[b]	n.r. 5 (5.5)	2.61 [0.71; 9.58] 0.148

Endpoint	Lisocabtagene maraleucel		Induction therapy + HDT + autoSCT		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 [a] Absolute difference (AD)[k]
Severe infections (SOC infections and infestations, CTCAE grade ≥ 3)[n]					
	92[b]	n.r. 14 (15.2)	91[b]	n.r. 19 (20.9)	0.62 [0.31; 1.27] 0.191
Diarrhoea (PT)					
	92[b]	n.r. 23 (25.0)	91[b]	3.3 [3.0; n.c.] 39 (42.9)	0.43 [0.26; 0.73] 0.002
Mucositis (PT)					
	92[b]	n.r. 5 (5.4)	91[b]	n.r. 14 (15.4)	0.25 [0.09; 0.70] 0.009
Gastrointestinal disorders (SOC, SAE)					
	92[b]	n.r. 2 (2.2)	91[b]	n.r. 8 (8.8)	0.18 [0.04; 0.90] 0.036
Acute kidney injury (PT, SAE)[s]					
	92[b]	n.r. 0 (0)	91[b]	n.r. 5 (5.5)	n.a. 0.015[p]
General disorders and administration site conditions (SOC, CTCAE grade ≥ 3)[n]					
	92[b]	n.r. 4 (4.3)	91[b]	n.r. 10 (11.0)	0.30 [0.09; 0.98] 0.046
Neutropenia (PT, CTCAE grade ≥ 3)[n]					
	92[b]	n.r. 6 (6.5)	91[b]	n.r. 0 (0)	n.a. 0.038[p]
Neutropenia (PT, CTCAE grade ≥ 3)[n]					
	92[b]	1.3 [1.15; 1.41] 75 (81.5)	91[b]	3.0 [1.9; n.c.] 47 (51.6)	1.80 [1.24; 2.6] 0.002 AD = -1.7 months

Endpoint	Lisocabtagene maraleucel		Induction therapy + HDT + autoSCT		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 [a] Absolute difference (AD)[k]
Lymphopenia (PT, CTCAE grade ≥ 3)[n]					
	92[b]	n.r. 24 (26.1)	91[b]	n.r. 9 (9.9)	3.14 [1.41; 7.00] 0.005
Febrile neutropenia (PT, CTCAE grade ≥ 3)[n]					
	92[b]	n.r. 11 (12.0)	91[b]	n.r. 21 (23.1)	0.43 [0.20; 0.90] 0.025
Thrombocytopenia (PT, CTCAE grade ≥ 3)[n]					
	92[b]	n.r. [1.8; n.c.] 46 (50.0)	91[b]	2.2 [1.2; 2.9] 62 (68.1)	0.60 [0.41; 0.89] 0.011

a Effect, CI and p value from Cox proportional hazards model, stratified by best overall response to first-line therapy (refractory [SD, PD, PR or CR with relapse < 3 months] vs relapsed [CR with relapse ≥ 3 and < 12 months]) and sAAIPI (0 or 1 vs 2 or 3), unless otherwise stated.
b The total population also includes adults with T-cell/ histiocyte-rich large B-cell lymphoma who are not part of the marketing authorisation population (n = 1 lisocabtagene maraleucel; n = 4 induction therapy + HDT+ autoSCT).
c Details of the pharmaceutical company from Annex 4J to Module 4B.
d No subgroup analyses are available for the lymphoma entity FL3B.
e Based on Cox proportional hazards model with treatment, subgroup feature and interaction term (treatment x subgroup feature)
f Unstratified cox proportional hazards model
g Information from the dossier of the pharmaceutical company.
h Since only the qualifying events are included in the event rate (total), the effect estimators of the individual components are not shown.
i Information from the Annex to the written statement of the pharmaceutical company.
j At the start of study, collections were only available for a small percentage of the randomised patients (around 54%). In addition, the percentage of missing values rises sharply over the course of the study and differs between the study arms. Due to discrepant information within the dossier, it remains unclear why there was a high percentage of missing values at the start of study. Without knowing the percentage of purely randomly missing values, it is not possible to judge whether the results are fundamentally interpretable. Therefore, the evaluations on the patient-reported endpoints presented by the pharmaceutical company in Module 4 B of the dossier are unsuitable for assessment.
k Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
l Operationalised via SAEs of the PT cytokine release syndrome (CRS). Operationalisation as severe AEs is not usable for this endpoint due to deviation from the severity grading according to CTCAE criteria and the associated discrepant results for SAEs.
m Operationalised via severe AEs (CTCAE grade ≥ 3) of the SOC nervous system disorders
n Operationalised via severe Aes (CTCAE grade ≥ 3)
o Effect: Mantel-Haenszel method; 95% CI and p value: Normal distribution approximation; stratified by best overall response to first-line therapy (refractory [SD, PD, PR or CR with relapse < 3 months] vs relapsed [CR with relapse ≥ 3 and < 12 months]) and sAAIPI (0 or 1 vs 2 or 3).
p p value based on log-rank test.

q Operationalised via AEs of the PT cytokine release syndrome. Information on the percentage of patients with an event and the result of the log-rank test are available for this endpoint. An effect estimate was not calculable using the Cox proportional hazards model presented by the pharmaceutical company. For the AEs of the higher-level SOC immune system disorders, which predominantly comprise PT cytokine release syndrome, the result is as follows: 51 (55.4%) vs 9 (9.9%); HR 6.96 [3.41; 14.18]; p < 0.001.

r Information on the percentage of patients with an event and the result of the log-rank test are available for this endpoint. An effect estimate was not calculable using the Cox proportional hazards model presented by the pharmaceutical company. For the SAEs of the higher-level SOC immune system disorders, which predominantly comprise the PT cytokine release syndrome, the result is as follows: 12 (13.0%) vs 2 (2.2%); HR: 5.91 [1.32; 26.48]; p = 0.020.

s Information on the percentage of patients with an event and the result of the log-rank test are available for this endpoint. An effect estimate was not calculable using the Cox proportional hazards model presented by the pharmaceutical company. For the higher-level SOC renal and urinary disorders, whose events predominantly comprise PT acute kidney injury (each operationalised as SAEs), the result is as follows: 1 (1.1) vs 7 (7.7); HR: 0.11 [0.01; 0.88]; p = 0.038.

Abbreviations used:
AD = absolute difference; autoSCT = autologous stem cell transplantation; BOR = best response; CR = complete response; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; DLBCL = diffuse large B-cell lymphoma; EORTC = European Organisation for Research and Treatment of Cancer; FACT-LymS = Functional Assessment of Cancer Therapy - Lymphoma Subscale; FL3B = follicular lymphoma grade 3B; HDT = high-dose therapy; HGBCL = high-grade B-cell lymphoma; HR = hazard ratio; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; NAT = new antineoplastic therapy; n.c. = not calculable; n.r. = not reached; QLQ-C30 = Quality of Life Questionnaire Cancer-30; PD = progressive disease; PFS = progression-free survival; PMBCL = primary mediastinal large B-cell lymphoma; PR = partial response; PT = preferred term; RR = relative risk; sAAIPI = secondary age-adjusted international prognostic index; SD = stable disease; SOC = system organ class; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs = versus

b1) Adults with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL) and follicular lymphoma grade 3B (FL3B), who are ineligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

No data are available to allow an assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data provided on mortality.
Morbidity	∅	No data provided on morbidity.
Health-related quality of life	∅	No data provided on quality of life.
Side effects	∅	No data provided on side effects.
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 ∅: No data available. n.a.: not assessable		

b2) Adults with primary mediastinal large B-cell lymphoma (PMBCL) who are ineligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

No data are available to allow an assessment of the additional benefit.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data provided on mortality.
Morbidity	∅	No data provided on morbidity.
Health-related quality of life	∅	No data provided on quality of life.
Side effects	∅	No data provided on side effects.
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 ∅: No data available. n.a.: not assessable		

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

a) Adults with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), who are eligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

approx. 835 – 1,180 patients

b1) Adults with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL) and follicular lymphoma grade 3B (FL3B), who are ineligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

approx. 820 – 1,150 patients

b2) Adults with primary mediastinal large B-cell lymphoma (PMBCL) who are ineligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

approx. 20 - 25 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 Breyanzi (active ingredient: lisocabtagene maraleucel) at the following publicly accessible link (last access: 9 October 2023):

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

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient emergency card. Training material for all healthcare professionals who will prescribe, dispense, and administer lisocabtagene maraleucel includes instructions for identifying, treating, and monitoring cytokine release syndrome and neurological side effects. It also includes instructions on the cell thawing process, availability of 1 dose of tocilizumab at the point of treatment, provision of relevant information to patients, and full and appropriate reporting of side effects.

The patient training programme should explain the risks of cytokine release syndrome and serious neurologic side effects, the need to report symptoms immediately to the treating physician, to remain close to the treatment facility for at least 4 weeks after infusion of lisocabtagene maraleucel and to carry the patient emergency card at all times.

Lisocabtagene maraleucel must be used in a qualified treatment facility. The quality assurance measures according to the ATMP Quality Assurance Guideline apply to the application of

lisocabtagene maraleucel in the therapeutic indication of large B-cell lymphoma as well as follicular lymphoma (FL). Annex I CAR-T cells in B-cell neoplasms of the ATMP Quality Assurance Guideline provides further details.

4. Treatment costs

Annual treatment costs:

The costs for the first year of treatment are shown for the cost representation in the resolution.

a) Adults with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), who are eligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Lisocabtagene maraleucel	€ 345,000.00
Additionally required SHI costs	*€ 744.76*
Appropriate comparator therapy:	
Induction chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation if there is a response to induction chemotherapy	
Induction chemotherapies	
R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin); 2-3 cycles	
Rituximab	€ 5,315.42 - € 8,313.20
Gemcitabine	€ 734.20 - € 1,101.30
Dexamethasone	€ 44.29 - € 79.59
Cisplatin	€ 228.06 - € 342.09
R-GDP	€ 6,321.97 - € 9,836.18
Additionally required SHI costs	*€ 143.16 - € 192.26*
R-ICE (rituximab + ifosfamide + carboplatin + etoposide); 2-3 cycles including a single dose of rituximab before the start of treatment	
Rituximab	€ 8,313.20 - € 10,630.84
Ifosfamide	€ 671.48 - € 1,007.22
Carboplatin	€ 633.30 - € 822.60 (2 cycles) – € 949.95 - € 1,233.90 (3 cycles)
Etoposide	€ 459.30 - € 688.95
R-ICE	€ 10,077.28 - € 10,266.58 (2 cycles) –

Designation of the therapy	Annual treatment costs/ patient
	€ 13,276.96 - € 13,560.91 (3 cycles)
Additionally required SHI costs	*€ 105.00 - € 433.37*
R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin); 2-3 cycles including **optional** single dose of rituximab before the start of treatment	
Rituximab	€ 5,315.42 - € 10,630.84
Dexamethasone	€ 44.29 - € 79.59
Cytarabine	€ 575.52 - € 863.28
Cisplatin	€ 285.96 - € 428.94
R-DHAP	€ 6,221.19 - € 12,002.65
Additionally required SHI costs	*€ 143.16 - € 192.26*
High-dose chemotherapy with autologous stem cell transplantation	
High-dose chemotherapy with autologous stem cell transplantation	€ 38,863.86
Total	
R-GDP induction chemotherapy + High-dose chemotherapy with autologous stem cell transplantation	€ 45,185.83 - € 48,700.04
Additionally required SHI costs	*€ 143.16 - € 192.26*
R-ICE induction chemotherapy + High-dose chemotherapy with autologous stem cell transplantation	€ 48,941.14 - € 49,130.44 (2 cycles R-ICE) – € 52,140.82 - € 52,424.77 (3 cycles R-ICE)
Additionally required SHI costs	*€ 105.00 - € 433.37*

Designation of the therapy	Annual treatment costs/ patient
R-DHAP induction chemotherapy + High-dose chemotherapy with autologous stem cell transplantation	€ 45,085.05 - € 50,866.51
Additionally required SHI costs	*€ 143.16 - € 192.26*
Induction chemotherapy followed by *high-dose chemotherapy with allogeneic stem cell transplantation if there is a response to induction chemotherapy*	
Induction chemotherapies	
R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin); 2-3 cycles	
Rituximab	€ 5,315.42 - € 8,313.20
Gemcitabine	€ 734.20 - € 1,101.30
Dexamethasone	€ 44.29 - € 79.59
Cisplatin	€ 228.06 - € 342.09
R-GDP	€ 6,321.97 - € 9,836.18
Additionally required SHI costs	*€ 143.16 - € 192.26*
R-ICE (rituximab + ifosfamide + carboplatin + etoposide); 2-3 cycles including a single dose of rituximab before the start of treatment	
Rituximab	€ 8,313.20 - € 10,630.84
Ifosfamide	€ 671.48 - € 1,007.22
Carboplatin	€ 633.30 - € 822.60 (2 cycles) – € 949.95 - € 1,233.90 (3 cycles)
Etoposide	€ 459.30 - € 688.95
R-ICE	€ 10,077.28 - € 10,266.58 (2 cycles) – € 13,276.96 - € 13,560.91 (3 cycles)
Additionally required SHI costs	*€ 105.00 - € 433.37*
R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin); 2-3 cycles including optional single dose of rituximab before the start of treatment	
Rituximab	€ 5,315.42 - € 10,630.84
Dexamethasone	€ 44.29 - € 79.59
Cytarabine	€ 575.52 - € 863.28
Cisplatin	€ 285.96 - € 428.94
R-DHAP	€ 6,221.19 - € 12,002.65
Additionally required SHI costs	*€ 143.16 - € 192.26*
High-dose chemotherapy with allogeneic stem cell transplantation	
High-dose chemotherapy with allogeneic stem cell transplantation	€ 57,563.63

Designation of the therapy	Annual treatment costs/ patient
Total	
R-GDP induction chemotherapy + High-dose chemotherapy with allogeneic stem cell transplantation	€ 63,885.60 - € 67,399.81
Additionally required SHI costs	*€ 143.16 - € 192.26*
R-ICE induction chemotherapy + High-dose chemotherapy with allogeneic stem cell transplantation	€ 67,640.91 - € 67,830.21 (2 cycles R-ICE) – € 70,840.59 - € 71,124.54 (3 cycles R-ICE)
Additionally required SHI costs	*€ 105.00 - € 433.37*
R-DHAP induction chemotherapy + High-dose chemotherapy with allogeneic stem cell transplantation	€ 63,784.82 - € 69,566.28
Additionally required SHI costs	*€ 143.16 - € 192.26*

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 November 2023)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed					
Lisocabtagene maraleucel - Lymphocyte depletion					
Cyclophosphamide	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	3	3.0	€ 300
Fludarabine	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	3	3.0	€ 300

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Appropriate comparator therapy					
Induction chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation if there is a response to induction chemotherapy					
Induction chemotherapies					
R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin); 2-3 cycles					
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	2.0 - 3.0	€ 200 - € 300
Gemcitabine	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	2	4.0 - 6.0	€ 400 - € 600
Cisplatin	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	1	2.0 - 3.0	€ 200 - € 300
R-ICE (rituximab + ifosfamide + carboplatin + etoposide); 2-3 cycles including a single dose of rituximab before the start of treatment					
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	3.0 - 4.0	€ 300 - € 400
Ifosfamide	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	1	2.0 - 3.0	€ 200 - € 300
Carboplatin	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	1	2.0 - 3.0	€ 200 - € 300
Etoposide	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	3	6.0 - 9.0	€ 600 - € 900

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Mesna	Surcharge for production of other parenteral solutions	€ 54	2	4.0 - 6.0	€ 216 - € 324
R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin); 2-3 cycles including optional single dose of rituximab before the start of treatment					
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	2.0 - 4.0	€ 200 - € 400
Cytarabine	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	2	4.0 - 6.0	€ 400 - € 600
Cisplatin	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	1	2.0 - 3.0	€ 200 - € 300
Induction chemotherapy followed by high-dose chemotherapy with allogeneic stem cell transplantation if there is a response to induction chemotherapy					
Induction chemotherapies					
R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin); 2-3 cycles					
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	2.0 - 3.0	€ 200 - € 300
Gemcitabine	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	2	4.0 - 6.0	€ 400 - € 600
Cisplatin	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	1	2.0 - 3.0	€ 200 - € 300

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
R-ICE (rituximab + ifosfamide + carboplatin + etoposide); 2-3 cycles including a single dose of rituximab before the start of treatment					
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	3.0 - 4.0	€ 300 - € 400
Ifosfamide	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	1	2.0 - 3.0	€ 200 - € 300
Carboplatin	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	1	2.0 - 3.0	€ 200 - € 300
Etoposide	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	3	6.0 - 9.0	€ 600 - € 900
Mesna	Surcharge for production of other parenteral solutions	€ 54	2	4.0 - 6.0	€ 216 - € 324
R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin); 2-3 cycles including optional single dose of rituximab before the start of treatment					
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	2.0 - 4.0	€ 200 - € 400
Cytarabine	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	2	4.0 - 6.0	€ 400 - € 600
Cisplatin	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	1	2.0 - 3.0	€ 200 - € 300

b1) Adults with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBL) and follicular lymphoma grade 3B (FL3B), who are ineligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Lisocabtagene maraleucel	€ 345,000.00
Additionally required SHI costs	*€ 744.76*
Appropriate comparator therapy:	
Polatuzumab vedotin + bendamustine + rituximab	
Polatuzumab vedotin	€ 61,470.36
Bendamustine	€ 6,023.10
Rituximab	€ 15,946.26
Total	€ 83,439.72
Additionally required SHI costs	*€ 62.65 - € 62.98*
Tafasitamab + lenalidomide	
Tafasitamab	€ 97,585.95
Lenalidomide	€ 427.76
Total	€ 98,013.71

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 November 2023)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed					
Lisocabtagene maraleucel - Lymphocyte depletion					
Cyclophosphamide	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	3	3.0	€ 300
Fludarabine	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	3	3.0	€ 300

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Appropriate comparator therapy					
Polatuzumab vedotin + bendamustine + rituximab					
Polatuzumab vedotin	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	6.0	€ 600
Bendamustine	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	2	12.0	€ 1,200
Rituximab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	6.0	€ 600
Tafasitamab + lenalidomide					
Tafasitamab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	Cycle 1: 5 Cycle 2 and 3: 4 From cycle 4 onwards: 2	33.0	€ 3,300

b2) Adults with primary mediastinal large B-cell lymphoma (PMBCL) who are ineligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Lisocabtagene maraleucel	€ 345,000.00
Additionally required SHI costs	*€ 744.76*
Appropriate comparator therapy:	
Pembrolizumab monotherapy	
Pembrolizumab	€ 93,515.26
Nivolumab + brentuximab vedotin	
Nivolumab	€ 48,690.42

Designation of the therapy	Annual treatment costs/ patient
Brentuximab vedotin	€ 159,283.60
Total	€ 207,974.02

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 November 2023)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Medicinal product to be assessed					
Lisocabtagene maraleucel - Lymphocyte depletion					
Cyclophosphamide	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	3	3.0	€ 300
Fludarabine	Surcharge for production of a parenteral solution containing cytostatic agents	€ 100	3	3.0	€ 300
Appropriate comparator therapy					
Pembrolizumab monotherapy					
Pembrolizumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4	€ 1,740
Nivolumab + brentuximab vedotin					
Nivolumab	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4	€ 1,740
Brentuximab vedotin	Surcharge for the preparation of a parenteral solution containing monoclonal antibodies	€ 100	1	17.4	€ 1,740

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

a) Adults with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), who are eligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

b1) Adults with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL) and follicular lymphoma grade 3B (FL3B), who are ineligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

b2) Adults with primary mediastinal large B-cell lymphoma (PMBCL) who are ineligible for high-dose therapy and relapsed within 12 months from completion of, or are refractory to, first-line therapy

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 November 2023.

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

Berlin, 16 November 2023

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

Prof. Hecken