Lisocabtagene maraleucel (Diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma and follicular lymphoma grade 3B, after ≥ 2 prior therapies)

Resolution of: 6 April 2023/ 1 June 2023 Valid until: unlimited
Entry into force on: 6 April 2023/ 1 June 2023
Federal Gazette, BAnz AT 19 05 2023 B10/ 23 06 2023 B5

Therapeutic indication (according to the marketing authorisation of 4 April 2022):

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy.

Therapeutic indication of the resolution (resolution of 6 April 2023):

See therapeutic indication according to marketing authorisation.

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

Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy

Appropriate comparator therapy for lisocabtagene maraleucel:

Patient-individual therapy with selection of:

- CEOP (cyclophosphamide, etoposide, vincristine, prednisone),
- dose-adjusted EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone),
- MINE (mesna, ifosfamide, mitoxantrone, etoposide),
- polatuzumab vedotin + bendamustine + rituximab (only for subjects with DLBCL who are ineligible for haematopoietic stem cell transplant),
- tafasitamab + lenalidomide (only for subjects with DLBCL who are ineligible for autologous stem cell transplant),
- pixantrone monotherapy,
- rituximab monotherapy (only for subjects with FL3B),
- tisagenlecleucel (only for subjects with DLBCL and FL3B),
- axicabtagene ciloleucel (only for subjects with DLBCL and PMBCL),
- radiation,
- stem cell transplant (autologous or allogeneic),
- or best supportive care;

taking into account the lymphoma subentity, biology of the disease, prior therapy, the course of the disease and the general condition.

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:[1]

Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable data.
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		

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

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

Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy

[1] Data from the dossier assessment of the IQWiG (A22-90) and from the addendum, unless otherwise indicated.

approx. 1,420 - 1,980 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: 22 February 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:

Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Lisocabtagene maraleucel[2]	
Lisocabtagene maraleucel	€ 345,000.00

2 It concerns only the cost of the medicinal product Breyanzi.

Designation of the therapy	Annual treatment costs/ patient
Additionally required SHI services[3]	
Lymphocyte depletion HBV, HCV and HIV screening Premedication	€ 724.33 € 20.15 incalculable
Appropriate comparator therapy:	
Cyclophosphamide + etoposide + vincristine + prednisone (CEOP)	
Cyclophosphamide	€ 543.90
Etoposide	€ 3,993.82
Vincristine	€ 598.21
Prednisone	€ 224.72
Total	€ 5,360.65
Etoposide + vincristine + doxorubicin + cyclophosphamide + prednisone (dose-adjusted EPOCH)	
Etoposide	€ 2,667.21
Vincristine	€ 1,488.05
Doxorubicin	€ 5,009.81
Cyclophosphamide	€ 543.90
Prednisone	€ 269.67
Total	€ 9,978.63
Mesna + ifosfamide + mitoxantrone + etoposide (MINE)	
Mesna	€ 609.30 - € 2,879.15
Ifosfamide	€ 4,717.05 - € 6,313.59
Mitoxantrone	€ 2,897.70 - € 3,878.46
Etoposide	€ 2,647.71 - € 3,543.86
Total	€ 10,871.76 - € 16,615.06
Polatuzumab vedotin + bendamustine + rituximab	
Polatuzumab vedotin	€ 68,524.20
Bendamustine	€ 6,044.01
Rituximab	€ 15,945.66
Total	€ 90,513.87
Additionally required SHI services	€ 61.66 - € 61.99
Tafasitamab + lenalidomide	
Tafasitamab	€ 97,579.35
Lenalidomide	€ 715.32
Total	€ 98,294.67

3 Since leukapheresis is part of the manufacture of the medicinal product pursuant to Section 4, paragraph 14 Medicinal Products Act (MPA), no further costs are incurred in this respect for the medicinal product to be assessed.

Designation of the therapy	Annual treatment costs/ patient
Pixantrone monotherapy	
Pixantrone	€ 5,575.80 - € 33,454.80
Rituximab monotherapy	
Rituximab	€ 10,630.44
Additionally required SHI services	€ 45.80 - € 46.13
Axicabtagene ciloleucel	
Axicabtagene ciloleucel[4]	€ 282,000.00
Additionally required SHI services[3]	€ 761.77
Tisagenlecleucel	
Tisagenlecleucel[5,]	€ 265,000.00
Additionally required SHI services[3]	€ 414.17
Radiation	
Radiotherapy	Different from patient to patient
Best supportive care	
Best supportive care[6]	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 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 preparation containing cytostatic agents	€ 100	3	3.0	€ 300
Fludarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	3.0	€ 300
Appropriate comparator therapy:					

4 It concerns only the cost of the medicinal product Yescarta.
5 It concerns only the cost of the medicinal product Kymriah.
6 In the case of a comparison with best supportive care, also to be used additionally for the medicinal product to be assessed.

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Cyclophosphamide + etoposide + vincristine + prednisone (CEOP)					
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Etoposide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	52.2	€ 5,220
Vincristine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Etoposide + vincristine + doxorubicin + cyclophosphamide + prednisone (dose-adjusted EPOCH)					
Etoposide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	4	69.6	€ 6,960
Vincristine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	4	69.6	€ 6,960
Doxorubicin	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	4	69.6	€ 6,960
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	1	17.4	€ 1,740
Mesna + ifosfamide + mitoxantrone + etoposide (MINE)					
Mesna	Surcharge for production of other parenteral solutions	€ 54	3	39.0 - 52.2	€ 2,106 - € 2,818.80
Ifosfamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	39.0 - 52.2	€ 3,900 - € 5,220
Mitoxantrone	Surcharge for production of a parenteral	€ 100	1	13.0 - 17.4	€ 1,300 - € 1,740

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	preparation containing cytostatic agents				
Etoposide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	39.0 - 52.2	€ 3,900 - € 5,220
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 preparation 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
Pixantrone monotherapy					
Pixantrone	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	3.0 - 18.0	€ 300 - € 1,800
Rituximab monotherapy					
Rituximab	Surcharge for the preparation of a parenteral solution	€ 100	1	4.0	€ 400

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
	containing monoclonal antibodies				
Axicabtagene ciloleucel					
Lymphocyte depletion					
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	3.0	€ 300
Fludarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	3.0	€ 300
Tisagenlecleucel					
Lymphocyte depletion					
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	3.0	€ 300
Fludarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	3.0	€ 300

5. 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 Lisocabtagene maraleucel

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients which are used in a combination therapy with lisocabtagene maraleucel for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) in adult patients after two or more lines of systemic therapy, on the basis of the marketing authorisation under Medicinal Products Act:

- No active ingredient 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.