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

of 6 April 2023

At its session on 6 April 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. Annex XII shall be amended in alphabetical order to include the active ingredient Lisocabtagene maraleucel as follows:**

**Lisocabtagene maraleucel**

Resolution of: 6 April 2023
Entry into force on: 6 April 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

**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:<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 | | |

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

approx. 1,420 - 1,980 patients

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

## 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 |
| Additionally required SHI services[3]<br><br>Lymphocyte depletion<br>HBV, HCV and HIV screening<br>Premedication | <br><br>€ 724.33<br>€ 20.15<br>incalculable |

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

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 |
|---|---|
| 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 |
| *Pixantrone monotherapy* | |
| Pixantrone | € 5,575.80 - € 33,454.80 |
| *Rituximab monotherapy* | |
| Rituximab | € 10,630.44 |
| Additionally required SHI services | € 45.80 - € 46.13 |

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| *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: | | | | | |
| *Cyclophosphamide + etoposide + vincristine + prednisone (CEOP)* | | | | | |
| Cyclophosphamide | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1 | 17.4 | € 1,740 |



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 |
|---|---|---|---|---|---|
| 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 preparation containing cytostatic agents | € 100 | 1 | 13.0 - 17.4 | € 1,300 - € 1,740 |
| Etoposide | Surcharge for production of a parenteral | € 100 | 3 | 39.0 - 52.2 | € 3,900 - € 5,220 |

| Designation of the therapy | Type of service | Costs/ unit | Number/ cycle | Number/ patient/ year | Costs/ patient/ year |
|---|---|---|---|---|---|
| | preparation containing cytostatic agents | | | | |
| *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 containing monoclonal antibodies | € 100 | 1 | 4.0 | € 400 |
| Axicabtagene ciloleucel | | | | | |
| Lymphocyte depletion | | | | | |

| Designation of the therapy | Type of service | Costs/ unit | Number/ cycle | Number/ patient/ year | Costs/ patient/ year |
|---|---|---|---|---|---|
| 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.

## II. Entry into force.

1. **The resolution will enter into force on the day of its publication on the website of the G-BA on 6 April 2023.**

2. **The period of validity of the resolution is limited to 15 October 2023.**

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

Berlin, 6 April 2023

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

Prof. Hecken