Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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 follicular lymphoma grade 3B; after 1 prior therapy, relapse within 12 months or refractory)

of 16 November 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. For medicinal products approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient lisocabtagene maraleucel (Breyanzi) was listed for the first time on 1 September 2022 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 28 April 2023, lisocabtagene maraleucel received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 30 May 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient lisocabtagene maraleucel with the new therapeutic indication*:* "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.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 September 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of lisocabtagene maraleucel compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of lisocabtagene maraleucel.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of Lisocabtagene maraleucel (Breyanzi) according to the product information

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

[1] General Methods, version 7.0 of 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

(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 16.11.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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 for lisocabtagene maraleucel:

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[2]

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 for lisocabtagene maraleucel:

Therapy according to doctor's instructions under consideration of

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

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

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 for lisocabtagene maraleucel:

- Pembrolizumab monotherapy

or

- Nivolumab in combination with brentuximab vedotin

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. In addition to lisocabtagene maraleucel, the following active ingredients are approved for the lymphoma entities covered by this therapeutic indication:
- The active ingredients bleomycin, carmustine, cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, ifosfamide, melphalan, methotrexate, methylprednisolone, mitoxantrone, pixantrone, prednisone, prednisolone, trofosfamide, vinblastine, vincristine and vindesinehave the marketing authorisation for the higher-level therapeutic indication "non-Hodgkin lymphoma".
- The active ingredients polatuzumab vedotin in combination with bendamustine and rituximab, tafasitamab in combination with lenalidomide, rituximab in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) and axicabtagene ciloleucel have the marketing authorisation for the treatment of diffuse large B-cell lymphoma (DLBCL) and high grade B-cell lymphoma (HGBCL) following first-line therapy.
- Rituximab is also approved as monotherapy for the treatment of stage III-IV follicular lymphoma in case of resistance to chemotherapy. Apart from lisocabtagene maraleucel, no other medicinal products are explicitly approved for the treatment of follicular lymphoma grade 3B (FL3B).
- Apart from lisocabtagene maraleucel, no other medicinal products are explicitly approved for the treatment of primary mediastinal large B-cell lymphoma (PMBCL) following first-line therapy.

The marketing authorisations mentioned are partly linked to (specified) concomitant active ingredients or do not fully cover the patient groups comprised by the present therapeutic indication.

on 2. In principle, autologous or allogeneic stem cell transplantation is considered as non-medicinal treatment in the present therapeutic indication. In addition, radiotherapy

can be administered, for example, to treat localised residual manifestations of the lymphoma after completion of chemotherapy.

on 3. For this therapeutic indication, there are the following resolutions or guidelines of the G-BA for medicinal applications or non-medicinal treatments:

Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Tafasitamab – resolution of 3 March 2022
- Polatuzumab vedotin – resolution of 20 August 2020
- Pixantrone – resolution of 16 May 2013

Guideline for Inpatient Treatment Methods (last revised 18 October 2023:

- Section 4 Excluded methods: Allogeneic stem cell transplantation in adult patients with aggressive B-non-Hodgkin lymphoma who have not yet been treated with autologous stem cell transplantation (exceptions: a) patients who have a very high risk of recurrence and who achieve a response at least in the sense of stable disease after salvage therapy; b) patients in whom sufficient stem cell harvesting for autologous stem cell transplantation was not possible and who achieve a response at least in the sense of stable disease after salvage therapy).
- Annex I: Methods required for hospital care: Allogeneic stem cell transplantation in adult patients with aggressive B-non-Hodgkin lymphoma who relapse after autologous stem cell transplantation and achieve a response at least in the sense of stable disease after salvage therapy.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V. A written statement from the German Society for Haematology and Medical Oncology (DGHO) is available.

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

The present patient population consists of adults with early relapse or refractoriness to first-line therapy.

The evidence-based therapy recommendations of the current guidelines[3,4,5] basically indicate that the therapy of relapsed or refractory patients with HGBCL and FL3B, as well as with PMBCL, in case of eligibility for high-dose therapy, is based on the treatment of patients with relapsed or refractory DLBCL. For patients with relapsed or refractory PMBCL who are ineligible for high-dose therapy, different therapy options are recommended in the current guidelines for DLBCL.

The present therapeutic indication generally refers to adults with DLBCL, HGBCL, PMBCL and FL3B who relapsed within 12 months from completion of, or are refractory to, first-line therapy, and is not restricted with regard to suitability or unsuitability for an intensive therapeutic approach. In the therapy recommendations relating to second-line therapy, the S3 guideline of the Oncology Guideline Programme[3] distinguishes between patients with early or late relapse who are eligible for high-dose therapy with the primary intention of curative treatment and second-line treatment of patients who are ineligible for high-dose therapy. This is also reflected in the present written statement from the German Society for Haematology and Medical Oncology. The S3 guideline also states that, in view of the availability of newer therapy options, the established categorisation into patients eligible for high-dose therapy and those ineligible for high-dose therapy is no longer expedient, but will continue to be used.

The statement of the scientific-medical societies on the present benefit assessment procedure indicates that in medical treatment practice, the criterion of patients' eligibility for high-dose therapy is no longer relevant in the case of early relapses or refractoriness to first-line therapy due to the availability of CAR-T cell therapies. In the current clinical healthcare context, patients are categorised according to their eligibility for CAR-T cell therapy in accordance with the statements of the scientific-medical societies.

The presented assessment of the scientific-medical societies that the criterion of "eligibility for high-dose therapy" is no longer relevant for patients with early relapse or refractoriness to first-line therapy in the current healthcare context is largely based on the pivotal study evidence on lisocabtagene maraleucel and axicabtagene ciloleucel in the treatment setting under assessment. However, this assessment is currently not adequately reflected in the current guideline recommendations. It is therefore considered appropriate by the G-BA to differentiate the patient groups according to their suitability for high-dose therapy when determining the appropriate comparator

3 Association of the Scientific-Medical Societies (AWMF). Diagnostics, therapy and after-care for adult patients with diffuse large B-cell lymphoma and related entities; S3-guideline [online]. AWMF register number 018-038OL. Berlin (GER): Oncology guideline programme; 2022.

4 National Institute for Health and Care Excellence (NICE). Non-Hodgkin's lymphoma: diagnosis and management [online]. 07.2021, last check 10.2021. London (GBR): NICE; 2016. (NICE Guideline; Band NG52).

5 National Comprehensive Cancer Network (NCCN). B-Cell lymphomas; Vers. 05.2022 [online]. Fort Washington (USA): NCCN; 2022. (NCCN Clinical Practice Guidelines in Oncology).

therapy for the present resolution on lisocabtagene maraleucel in accordance with the currently valid guideline recommendations.

Taking into account the specific therapy recommendations for the lymphoma entities covered by this therapeutic indication, the following patient groups result:

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

If patients with an early relapse are eligible for high-dose therapy based on their general condition or comorbidity, CAR-T cell therapies are the main treatment strategy according to the available guidelines and statements of the scientific-medical societies. The CAR-T cell therapies axicabtagene ciloleucel or lisocabtagene maraleucel are recommended in the current guidelines.

The CAR-T cell therapies axicabtagene ciloleucel and lisocabtagene maraleucel are gene therapies. Autologous T cells are genetically modified by the introduction of a chimeric antigen receptor. The chimeric antigen receptor of axicabtagene ciloleucel and lisocabtagene maraleucel targets the same surface antigen, cluster of differentiation 19 (CD19).

The mode of action of CAR-T cells differs from the mode of action of the treatment options previously used in this therapeutic indication. As part of chemoimmunotherapy, cytostatic agents or anti-CD-20 antibodies are used for B-cell lymphoma, which do not constitute gene therapy. Although the subsequent stem cell transplantation is also based on a cellular or immunological mode of action, autologous or allogeneic stem cells, which have not been genetically modified and therefore do not act on a specific surface antigen, are infused to rebuild haematopoiesis. Therefore, chemoimmunotherapy is usually required to eliminate the malignant lymphoma cells before performing stem cell transplantation for B-cell lymphoma, whereas CAR-T cell therapy can also be used without prior chemoimmunotherapy.

Overall, it can be stated that the CAR T-cell therapy procedure shows relevant differences to the previous treatment standard with regard to the various therapy steps. In addition, suitability for high-dose therapy with autologous or allogeneic stem cell transplantation is not the same as patients' suitability for CAR-T cell therapy, which in principle represents a possible therapy option for a larger patient population.

While the product class of CAR-T cell therapies for the treatment of B-cell lymphomas has been established in healthcare for some time after at least two prior therapies, axicabtagene ciloleucel and lisocabtagene maraleucel were only recently approved for the second-line treatment of B-cell lymphomas in close proximity to each other. In addition, the benefit assessment procedure for axicabtagene ciloleucel has been

ongoing since 1 July 2023, meaning that its patient-relevant additional benefit has not yet been determined by the G-BA. For the therapeutic indication under assessment, the product class of CAR-T cell therapies is thus a new treatment option that should be compared with the same appropriate comparator therapy in accordance with Section 6 paragraph 3 AM-NutzenV in conjunction with Chapter 5 Section 6, paragraph 5, sentence 1 VerfO in order to ensure a standardised assessment.

According to Section 6, paragraph 2, sentence 2 AM-NutzenV, the determination of the appropriate comparator therapy must also be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. Effects on the medical treatment situation that only result from the addition of the new medicinal product must be disregarded.

In the overall assessment of the aspects presented, the G-BA considers it necessary for the determination of the appropriate comparator therapy in the present resolution on lisocabtagene maraleucel to disregard the effects on the medical treatment situation resulting overall from the addition of the product class of CAR-T cells, which includes both lisocabtagene maraleucel and axicabtagene ciloleucel.

In this particular case constellation, the G-BA considers it appropriate to base the determination of the appropriate comparator therapy for the considered patient group on the treatment standard that would result without the addition of the CAR-T cell therapies to be assessed.

According to the available guidelines, prior to the availability of CAR-T cell therapies, platinum-based induction chemotherapy, consolidated by high-dose therapy with autologous stem cell transplantation in case of response (complete remission (CR) or partial remission (PR)), was considered the therapy standard for all adults eligible for high-dose therapy with relapsed or refractory DLBCL, HGBCL, FL3B and PMBCL following first-line therapy. In addition, allogeneic stem cell transplantation can be considered as consolidation in accordance with the Guideline for Inpatient Treatment Methods[6], provided that the patient has achieved a response after salvage therapy that is at least equivalent to stable disease and the patient has a very high risk of relapse or it was not possible to harvest sufficient stem cells for autologous stem cell transplantation.

According to the current guidelines, the treatment regimens GDP (gemcitabine, dexamethasone, cisplatin or carboplatin), DHAP (dexamethasone, cisplatin, cytarabine) and ICE (ifosfamide, carboplatin, etoposide), each in combination with rituximab, are specifically recommended as platinum-based induction chemotherapy. In accordance with the S3 guideline recommendations, these treatment regimes were compared with each other in prospective randomised studies, whereby differences in

[6] Last revised 18 October 2023

toxicity were found with the same efficacy.[7,8] According to the scientific-medical societies, these three combination therapies represent the standard of care and have proven to be equivalent in the context of induction therapy. The protocols R-GDP, R-DHAP and R-ICE have already been used as standard protocols for induction therapy in this therapeutic indication as part of the G-BA's assessment of the "allogeneic stem cell transplantation for B-cell non-Hodgkin lymphomas" method.[9] Rituximab is approved in the present indication but only in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), and individual components of the combination therapies mentioned (cisplatin, carboplatin, gemcitabine) are also not approved in the present indication.

Of the active ingredients approved for the treatment of non-Hodgkin lymphoma, only the platinum-free induction therapy MINE (mesna, ifosfamide, mitoxantrone, etoposide), which is mentioned in the American guideline of the National Comprehensive Cancer Network (NCCN) as another possible treatment regimen of lower priority, is available[5]. The statements of clinical experts in the present benefit assessment procedure indicate that MINE has no relevant significance in the present therapeutic indication and any sporadic use in the past was consolidated with a platinum-containing therapy. In agreement with the estimate of the clinical experts, all the available guidelines unanimously recommend platinum-containing induction therapy with R-GDP, R-ICE or R-DHAP, although it should be noted that the platinum-free induction therapy MINE is not mentioned at all in the S3 guideline relevant especially to the German healthcare context.

Taking into account the present evidence, the use of induction therapy with R-GDP, R-DHAP or R-ICE is generally preferable to induction therapy with MINE for the considered patient group in accordance with Section 6, paragraph 2, sentence 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). For the determination of the appropriate comparator therapy in the present resolution on lisocabtagene maraleucel, it is necessary to disregard the overall effects on the medical treatment situation resulting from the addition of the product class of CAR-T cells. Therefore, it is appropriate to determine the off-label use of the above-mentioned combinations of medicinal products as the appropriate comparator therapy for the present patient population. The other approved active ingredients listed under paragraph 1 do not correspond to the therapy recommendations for the indication in

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7 Gisselbrecht C, Glass B, Mounier N, Linch D, Gill D, Trneny M. R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by autologous stem cell transplantation: CORAL study. 2009;27:15s

8 Crump M, Kuruvilla J, Couban S, MacDonald D, Kukreti V, Kouroukis C, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY12. J Clin Oncol. 2014;32:3490-6.

9 Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Guideline for Inpatient Treatment Methods: Allogeneic stem cell transplantation for aggressive B-cell non-Hodgkin lymphomas; 9 April 2020

question and do not correspond to the therapy standard in the medical treatment situation according to Section 6, paragraph 2, sentence 2 AM-NutzenV as it would be without CAR-T cell therapies, as set out in the guidelines and in the statement of the scientific-medical societies.

In the overall assessment, induction therapy with R-GDP, R-ICE *or* R-DHAP followed by high-dose therapy with autologous or allogeneic stem cell transplantation is determined to be an appropriate comparator therapy for the present patient group if there is a response to induction therapy.

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

This patient group comprises adults with DLBCL, HGBCL and FL3B who are ineligible for high-dose therapy. According to the available guideline recommendations and the statements of the clinical experts in this benefit assessment procedure, adults with relapsed or refractory HGBCL and FL3B are treated according to the relapsed or refractory DLBCL.

The more recent guidelines[3,5] unanimously recommend polatuzumab in combination with bendamustine and rituximab, tafasitamab in combination with lenalidomide and less intensive immunochemotherapy protocols, for example rituximab in combination with gemcitabine and oxaliplatin (R-GemOx), as therapy options.

The antibody-drug conjugate polatuzumab vedotin is approved in combination with bendamustine and rituximab for the treatment of adults with relapsed or refractory DLBCL if they are ineligible for haematopoietic stem cell transplantation. By resolution of 20 August 2020, a hint for a non-quantifiable additional benefit over bendamustine in combination with rituximab was identified for polatuzumab vedotin within the scope of an orphan drug assessment because the scientific data did not allow quantification.

The CD19-specific antibody tafasitamab is approved in combination with lenalidomide for the treatment of patients with relapsed or refractory DLBCL for who are ineligible for autologous stem cell transplantation. By resolution of 3 March 2022, a hint for a non-quantifiable additional benefit was identified for tafasitamab within the scope of an orphan drug assessment because the scientific data did not allow quantification.

With regard to less intensive immunochemotherapies, the available evidence mentions the combination therapy R-GemOx in particular as a further treatment option, but it is not approved for this indication. It cannot be inferred from the available evidence that, according to the generally recognised state of medical knowledge, the off-label use of R-GemOx is generally preferable to the medicinal

products previously approved in the therapeutic indication or, for relevant patient groups or indication areas, to the medicinal products previously approved in the therapeutic indication. R-GemOx is therefore not determined to be an appropriate comparator therapy.

Since October 2022, the CAR-T cell therapy axicabtagene ciloleucel has been another approved therapy option for patients with DLBCL and HGBCL who are ineligible for high-dose therapy. The benefit assessment procedure for axicabtagene ciloleucel in the second-line treatment of early relapses or refractoriness has been ongoing since 1 July 2023. According to the statements of the scientific-medical societies, CAR-T cells are also a relevant therapy option for patients who are ineligible for high-dose therapy. However, the German S3 guideline does not include a recommendation for the use of axicabtagene ciloleucel in the second-line treatment of patients who are ineligible for high-dose therapy. In addition, reference is made to the above statements on patient group a), according to which it is necessary for the determination of the appropriate comparator therapy in the present resolution on lisocabtagene maraleucel to disregard the effects on the medical treatment situation resulting overall from the addition of the product class of CAR-T cells, which includes both lisocabtagene maraleucel and axicabtagene ciloleucel. Axicabtagene ciloleucel is therefore not determined to be an appropriate comparator therapy.

The available evidence shows that the therapy options polatuzumab in combination with bendamustine and rituximab as well as tafasitamab in combination with lenalidomide cannot be considered equally suitable for all patients included in the therapeutic indication, taking into account comorbidities and, if applicable, previous therapy and the further course of therapy. Therefore, in the overall assessment, a therapy according to doctor's instructions, taking into account polatuzumab in combination with bendamustine and rituximab and tafasitamab in combination with lenalidomide, is determined as the appropriate comparator therapy for adults with DLBCL, HGBCL and FL3B who are ineligible for high-dose therapy.

It should be noted here that the HGBL was only listed as a definitive entity with the WHO classification from June 2022 and has since been explicitly named by the EMA within the framework of the marketing authorisation.[10] Prior to this update, HGBCLs were subsumed under DLBCLs. The G-BA therefore considers it appropriate to consider treatment options that were approved before the WHO classification was updated in June 2022 when determining the appropriate comparator therapy for both DLBCL and HGBCL.

Polatuzumab in combination with bendamustine and rituximab and tafasitamab in combination with lenalidomide are not approved for the treatment of FL3B. FL3B is a

[10] Alaggio, R., Amador, C., Anagnostopoulos, I. et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukaemia 36; 1720-1748 (2022)

very rare lymphoma entity that is categorised as an aggressive B-cell lymphoma. The evidence on specific treatment options for FL3B is extremely limited. There are no therapy options specifically named for FL3B in the current guidelines, but they unanimously recommend that FL3B should be treated in the same way as DLBCL.[3,5] In line with the guideline recommendations, the clinical assessment experts refer to the use of DLBCL-typical treatment regimens, in particular polatuzumab in combination with bendamustine and rituximab as well as tafasitamab in combination with lenalidomide.

Apart from the active ingredient lisocabtagene maraleucel under assessment, no other active ingredients are explicitly approved for FL3B in the present treatment setting. Rituximab as monotherapy is generally approved for the treatment of stage III-IV follicular lymphoma that is resistant to chemotherapy. However, according to the statement of the clinical experts in this benefit assessment procedure, CD20 antibody monotherapies are ineffective in aggressive B-cell lymphomas such as FL3B and do not represent a therapy standard. The other active ingredients generally approved for non-Hodgkin lymphoma and listed under paragraph 1 also do not correspond to the therapy recommendations for the treatment of FL3B and to the therapy standard in the reality of care as set out in the guidelines and in the statement of the scientific-medical societies.

Based on the unanimous recommendations from the current guidelines and the statement of the clinical experts in the present benefit assessment procedure, it can be stated that for patients with relapsed or refractory FL3B who are ineligible for high-dose therapy, the off-label use of polatuzumab in combination with bendamustine and rituximab as well as tafasitamab in combination with lenalidomide is generally preferable to the medicinal products previously approved in the therapeutic indication according to the generally recognised state of medical knowledge. Taking into account the severity of the disease in relapsed or refractory FL3B, it is therefore appropriate to determine polatuzumab in combination with bendamustine and rituximab as well as tafasitamab in combination with lenalidomide as an appropriate comparator therapy in the off-label use for FL3B, Section 6, paragraph 2, sentence 3, no. 2 AM-NutzenV.

b2) <u>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</u>

Apart from lisocabtagene maraleucel, no active ingredients are explicitly approved for the treatment of patients with PMBCL who are ineligible for high-dose therapy following first-line therapy.

The statement of the clinical experts in the present benefit assessment procedure shows that therapy failure in PMBCL occurs almost exclusively during or immediately after primary therapy, so that the majority of patients have refractory disease. The

current guidelines recommend the use of a PD-1 inhibitor, possibly in combination with brentuximab vedotin, in patients with refractory PMBCL following first-line therapy.[3],[5] These recommendations are based on single-arm studies on pembrolizumab as monotherapy as well as for nivolumab in combination with brentuximab vedotin after at least 2 prior therapies.[11,12,13] The current S3 guideline recommendations represent an expert consensus (strong consensus) and are in line with the recommendations of the American NCCN guideline, the written statement of the DGHO and the statement of the clinical experts in the present benefit assessment procedure. It is therefore unanimous that the use of pembrolizumab as monotherapy or nivolumab in combination with brentuximab vedotin should be regarded as the current therapy standard for this patient group. However, pembrolizumab as monotherapy and nivolumab in combination with brentuximab are not approved for the treatment of relapsed or refractory PMBCL that relapses within 12 months from the completion of, or is refractory to, first-line therapy.

The combination chemotherapies CEOP (cyclophosphamide, etoposide, vincristine, prednisone) and dose-adjusted EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone) are also available for patients with PMBCL in accordance with the generic marketing authorisation of the individual active ingredients for non-Hodgkin lymphoma. However, CEOP and dose-adjusted EPOCH are only mentioned in the American NCCN guideline[5] as other possible treatment regimens, particularly for patients with DLBCL who are ineligible for high-dose therapy. It follows from the current guideline recommendations that CEOP and dose-adjusted EPOCH are not to be regarded as the therapy standard for the treatment of relapsed or refractory PMBCL in patients who are ineligible for high-dose therapy.[3,5] In addition, according to the statement of the clinical experts in the present benefit assessment procedure, the combination therapies mentioned are generally not considered in everyday care because the active ingredients contained in these combination therapies are already used in the CHOP-based standard therapy in the first line and no efficacy of these active ingredients or combinations of the active ingredients is to be expected in CHOP-refractory patients. The other approved active ingredients listed under paragraph 1 also do not correspond to the therapy recommendations for the treatment of relapsed or refractory PMBCL and to the therapy standard in the reality

[11] Armand P et al. Pembrolizumab in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma. J Clin Oncol. 2019 Dec 1;37(34):3291-3299. doi: 10.1200/JCO.19.01389. Epub 2019 Oct 14. PMID: 31609651; PMCID: PMC6881098.

[12] Zinzani PL et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. Blood. 2017 Jul 20;130(3):267-270. doi: 10.1182/blood-2016-12-758383. Epub 2017 May 10. PMID: 28490569; PMCID: PMC5766837.

[13] Zinzani PL et al. Nivolumab Combined With Brentuximab Vedotin for Relapsed/Refractory Primary Mediastinal Large B-Cell Lymphoma: Efficacy and Safety From the Phase II CheckMate 436 Study. J Clin Oncol. 2019 Nov 20;37(33):3081-3089. doi: 10.1200/JCO.19.01492. Epub 2019 Aug 9. PMID: 31398081; PMCID: PMC6864847.

of care as set out in the guidelines and in the statement of the scientific-medical societies.

PMBCL is a very rare lymphoma entity that accounts for around 2-4% of all non-Hodgkin lymphomas. Due to the high efficacy of first-line therapy, there is also only a small number of primary refractory or relapsed patients. Accordingly, the evidence for therapy recommendations is extremely limited. However, based on the unanimous recommendations of current guidelines and the statement of the clinical experts in the present benefit assessment procedure, it can be stated that for patients with relapsed or refractory PMBCL, the off-label use of pembrolizumab as monotherapy or nivolumab in combination with brentuximab vedotin is generally preferable to the medicinal products previously approved in the therapeutic indication according to the generally recognised state of medical knowledge. Taking into account the severity of the disease of relapsed or refractory PMBCL, it is therefore appropriate to determine pembrolizumab as monotherapy and nivolumab in combination with brentuximab vedotin as appropriate comparator therapy in the off-label use for PMBCL, Section 6, paragraph 2, sentence 3, number 2 AM-NutzenV.

Therefore, pembrolizumab as monotherapy or nivolumab in combination with brentuximab vedotin is determined to be an equally appropriate comparator therapy for patients with PMBCL who are ineligible for high-dose therapy.

The determination of the off-label use of medicinal products as an appropriate comparator therapy by resolution on the benefit assessment according to Section 35a paragraph 3 SGB V does not affect the procedure according to Section 35c SGB V.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

Change of the appropriate comparator therapy

The appropriate comparator therapy was originally determined as follows:

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 for lisocabtagene maraleucel:

- Induction therapy with MINE (mesna, ifosfamide, mitoxantrone, etoposide) followed by high-dose therapy with autologous or allogeneic stem cell transplantation if there is a response to induction therapy

b1) Adults with diffuse large B-cell lymphoma (DLBCL) and high grade B-cell lymphoma (HGBCL) who are **not** eligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

Appropriate comparator therapy for lisocabtagene maraleucel:

Therapy according to doctor's instructions under consideration of

- Pola-BR (polatuzumab in combination with bendamustine and rituximab)
- Tafasitamab + lenalidomide

b2) Adults with primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) who are **not** eligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy

Appropriate comparator therapy for lisocabtagene maraleucel:

Therapy according to doctor's instructions under consideration of

- CEOP (cyclophosphamide, etoposide, vincristine, prednisone)
- dose-adjusted EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone)
- rituximab monotherapy (only for subjects with FL3B)

This appropriate comparator therapy was determined for the present benefit assessment procedure on lisocabtagene maraleucel under the effects of the ruling of the Federal Social Court (FSC) of 22 February 2023. According to the FSC's comments on this ruling (file ref.: B 3 KR 14/21 R), medicinal products that do not have a marketing authorisation for the present indication and whose prescribability in off-label use has also not been recognised by the G-BA in the Pharmaceuticals Directive are generally not considered as appropriate comparator therapy in the narrower sense of Section 2, paragraph 1, sentence 3, Section 12 SGB V.

Within the scope of this provision, it was to be noted that medicinal therapies not approved for the treatment of DLBCL, HGBCL, PMBCL and FL3B who relapse within 12 months from completion of, or are refractory to, first-line therapy are mentioned in the current guidelines or by scientific-medical societies and/or the AkdÄ (Drugs Commission of the German Medical Association) according to Section 35a, paragraph 7, sentence 4 SGB V.

With the entry into force of the ALBVVG (Act to Combat Supply Shortages and Improve the Supply of Medicines) on 27 July 2023, the G-BA can exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy in accordance with Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV).

In view of the fact that for the present benefit assessment of lisocabtagene maraleucel, off-label use of medicinal products can be considered as an appropriate comparator therapy, also taking into account the statements of scientific-medical societies in the present procedure, a review of the appropriate comparator therapy under the regulations after the entry into force of the ALBVVG was necessary. In the course of this, the appropriate comparator therapy was changed for the present resolution.

This change means that the results of the TRANSFORM study submitted by the pharmaceutical company in the dossier can be used for the present assessment for patient group a). The TRANSFORM study was presented in IQWiG's dossier assessment. In addition, the results of the TRANSFORM study were the subject of the statements, which is why the change in the appropriate comparator therapy does not necessitate a renewed conduct of the benefit assessment procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of lisocabtagene maraleucel is assessed as follows:

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

Hint for a considerable additional benefit

Justification:

For the benefit assessment, the pharmaceutical company presented both the results of the phase III TRANSFORM study and an adjusted indirect comparison according to Bucher et al. of lisocabtagene maraleucel (Liso-Cel) versus axicabtagene ciloleucel (Axi-Cel; phase III ZUMA-7 study) for the total population of the new therapeutic indication. The pharmaceutical company does not differentiate between different research questions or patient groups depending on the suitability of the patients for high-dose therapy.

The presented adjusted indirect comparison is not used for the benefit assessment, as axicabtagene ciloleucel is not defined as an appropriate comparator therapy for the present resolution.

The study data from the phase III TRANSFORM study will be used to assess the additional benefit of Liso-Cel in adults with DLBCL, HGBCL, PMBCL and FL3B who are eligible for high-dose therapy and relapse within 12 months from completion of, or are refractory to, first-line therapy.

TRANSFORM study

In the ongoing, open-label phase III TRANSFORM study, Liso-Cel is being compared with induction therapy with R-GDP, R-ICE or R-DHAP followed by high-dose therapy (HDT) with autologous stem cell transplantation (autoSCT).

The study enrolled adults with DLBCL, HGBCL, PMBCL, FL3B and T-cell/histiocyte-rich large B-cell lymphoma (THRBCL). The patients enrolled had refractory or relapsed disease within 12 months of completing first-line chemoimmunotherapy, which had to include a CD20 antibody and an anthracycline. In addition, patients had to be eligible for high-dose therapy, be 75 years of age or older, have an ECOG status of 0-1 and adequate organ function. Patients with THRBCL are not part of the authorisation population and are therefore not considered further in the benefit assessment.

A total of 184 patients were randomised in a 1:1 ratio to the two study arms (N = 92 Liso-Cel; N = 92 induction + HDT + autoSCT). Randomisation was stratified according to response to first-line therapy (relapsed vs refractory) and according to the secondary age-adjusted international prognostic index (sAAIPI; 0-1 vs 2-3).

The study treatment included leukapheresis for the collection of peripheral mononuclear blood cells from all patients at the time of enrolment in the study. For the Liso-Cel arm, lymphocyte depletion and subsequent infusion of Liso-Cel followed the preparation of Car-T cells. In the period between randomisation and lymphocyte depletion, a bridge therapy in the form of chemoimmunotherapy (1 cycle of R-GDP, R-DHAP or R-ICE) or local radiotherapy could be used if necessary. In the comparator arm, patients received three cycles of induction chemoimmunotherapy with R-GDP, R-ICE or R-DHAP. Patients who achieved a partial or complete response according to the Lugano criteria (Cheson et al.; 2014) at week 9 after randomisation subsequently received HDT with an autosCT. Patients in the comparator arm who did not achieve at least a partial response at week 9 could receive Liso-Cel as subsequent therapy.

The mean age of the patients enrolled in the study was 56 years, with mainly adults aged < 65 years being enrolled. The percentage of adults aged 65 years and over is unevenly distributed between the study arms and is 39% and 27% respectively. The study predominantly enrols patients with DLBCL (approx. 64%), followed by patients with HGBCL (approx. 24%), PMBCL (approx. 8%) and FL3B (1 patient). In addition, the majority of patients had refractory disease

and a sAAIPI index of 0-1 at the start of study. A total of only 5 patients with THRBCL (approx. 3%) were enrolled, so that the total population of the TRANSFORM study is considered for the benefit assessment.

The study has been conducted in 53 study sites in Europe, Asia and the USA since October 2018. The primary endpoint of the study is event-free survival (EFS). Results are also available for other endpoints in the categories of mortality, morbidity, health-related quality of life and side effects.

Four data cut-offs have been carried out so far, with the pharmaceutical company using the 4th data cut-off from 13.05.2022 in the dossier. This is the pre-specified primary analysis of the TRANSFORM study, which was planned after 119 events were reached in the EFS endpoint and was conducted after 115 events had occurred. The data cut-off from 13.05.2022 is used as the basis for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

The overall survival was operationalised as the time from randomisation to death from any cause. There is no statistically significant difference between the treatment arms.

There is an effect modification for the age characteristic (< 65 years vs ≥ 65 years). For patients < 65 years of age, there is a statistically significant difference in favour of Liso-Cel, while for patients ≥ 65 years of age there is no statistically significant difference.

In the present benefit assessment procedure, the age limit of 65 years was estimated to be arbitrary by the scientific-medical societies. According to the statement of the clinical experts, the medical treatment decision is primarily based on the patient's general condition and existing comorbidities and is not made solely on the basis of age. A rigid age limit for the separate derivation of an additional benefit (adults < 65 years or ≥ 65 years) therefore appears to be inappropriate.

In the overall analysis of the available results from the TRANSFORM study, the effect modification by the age characteristic is considered insufficient to derive corresponding separate statements on the additional benefit in the overall assessment. The data on the subgroups < 65 years und ≥ 65 years are nevertheless considered a relevant outcome of the benefit assessment and are therefore shown in the study results.

Morbidity

Failure of the curative therapeutic approach

Patients in the present therapeutic indication are treated with a curative therapeutic approach. The failure of a curative therapeutic approach is fundamentally patient-relevant.

The event-free survival (EFS) endpoint from the TRANSFORM study is used as an approximation to illustrate the failure of the curative therapeutic approach. The significance

of the EFS endpoint depends on the extent to which the selected individual components are suitable for adequately reflecting the failure of potential cure by the present curative therapy approach.

In the TRANSFORM study, EFS was defined as the time from randomisation to the first occurrence of one of the following events:

- Death from any cause
- Disease progression
- Failure to achieve a CR or PR at week 9 after randomisation
- Start of a new antineoplastic therapy due to efficacy concerns

With regard to the component "initiation of renewed antineoplastic therapy due to efficacy concerns", it remains unclear whether this event per se represents a failure of the curative therapeutic approach without disease progression having previously been identified as a qualifying event. The study documents show that the predominant reasons for initiating renewed antineoplastic therapy were progression or existing residual disease that prevented stem cell transplantation. These events are included separately as qualifying events in the composite endpoint. In addition, the initiation of renewed antineoplastic therapy was only occasionally categorised as an EFS event (< 6%). The uncertainties associated with the individual component of initiating renewed antineoplastic therapy due to efficacy concerns are therefore considered negligible in the present case.

The components death from any cause, disease progression and failure to achieve a CR or PR at week 9 after randomisation are considered appropriate to reflect the failure of the curative therapeutic approach. However, these components only approximate the failure of the curative therapeutic approach, as the failure to achieve a CR at the end of treatment (in this case the time of the collection at week 18 after randomisation) also represents a failure of the curative therapeutic approach. This single component is not considered in the operationalisation of the EFS endpoint presented in the dossier.

With the written statement, the pharmaceutical company subsequently submitted evaluations on the EFS endpoint, in which the failure to achieve a CR at week 18 after randomisation is assessed as an additional qualifying event. These evaluations are suitable as an operationalisation of the failure of the curative therapeutic approach and are used for the present benefit assessment. For the assessment, the percentage of patients with an event (event rate) as well as the time-dependent evaluations (EFS) are considered.

There is a statistically significant difference in favour of Liso-Cel in both operationalisations. There are differences in the extent of the effect between the operationalisations of event rate and EFS, with a larger effect being observed for the time-to-event analysis.

Taking both operationalisations into account, the overall advantage in the failure of the curative therapeutic approach is assessed as a significant improvement for this patient group.

Symptomatology

In the dossier, the pharmaceutical company presents evaluations of the symptomatology collected using the symptom scales of the EORTC-QLQ-C30 questionnaire and the FACT-LymS questionnaire, but does not use these evaluations to derive the additional benefit. The pharmaceutical company justifies this with the insufficient reliability of the results due to the high percentage of missing values at the start of study.

In the dossier, the pharmaceutical company submits evaluations that only include patients for whom a follow-up value is available in addition to a value at the start of study. Only 50% of patients are considered in the evaluation. In addition, the percentage of missing values increases strongly and differentially between the study arms over the course of the study.

The reasons for the missing values cannot be clearly deduced from the study documents and the information in the dossier. The pharmaceutical company cited both limitations caused by the COVID pandemic and logistical obstacles in connection with the implementation of an electronic data collection system as the reasons for this. The pharmaceutical company was unable to provide an evaluation of the reasons that would allow an assessment of the percentage of values missing purely by chance and those missing for potentially informative reasons as part of the written statement procedure.

There are therefore no suitable data available for symptomatology overall.

Health status

The health status was assessed in the TRANSFORM study using the EQ-5D visual analogue scale (VAS). The pharmaceutical company does not use the results on the health status endpoint to derive the additional benefit due to the high percentage of missing values.

Please refer to the above statements on symptomatology. As the return rates were already < 70% at the start of study, no suitable data are available for the health status endpoint.

Quality of life

Quality of life was assessed in the TRANSFORM study using the functional scales of the EORTC-QLQ-C30 questionnaire. The pharmaceutical company does not use the results of the functional scales of the EORTC-QLQ-C30 questionnaire to derive the additional benefit due to the high percentage of missing values.

Reference is made to the above statements on the symptomatology endpoint. As the return rates were already < 70% at the start of study, no suitable data are available for quality of life.

Side effects

In the TRANSFORM study, adverse events were observed up to 90 days after infusion of Liso-Cel or the last dose of chemoimmunotherapy or until the start of subsequent antineoplastic therapy, whichever occurred first. In addition, adverse events which were reported to the principal investigators and which they consider to be a consequence of the study treatment

are also recorded up to 36 months after randomisation, regardless of their time of occurrence. From the G-BA's point of view, the period of up to 90 days after infusion of Liso-Cel for the standardised recording of adverse events appears relatively short in comparison to other clinical studies on CAR-T cell therapies in the indication B-cell lymphoma.

Adverse events (AEs, total)

In the TRANSFORM study, AEs occurred in both study arms in almost all patients. The results were only presented additionally.

Serious adverse events (SAEs) and severe adverse events (CTCAE grade ≥ 3)

There was no statistically significant difference between the study arms for the overall rate of serious AEs (SAEs) and severe AEs with CTCAE grade ≥ 3.

Discontinuation due to AEs

The therapy could only be discontinued for a short period at the start of the study. For the endpoint of discontinuation due to AEs, no statistically significant difference is detected between the study arms.

Specific adverse events

With regard to the specific AEs, there is a statistically significant advantage of Liso-Cel for the endpoints of diarrhoea, mucositis, gastrointestinal disorders (SAE), acute kidney injury (SAE), general disorders and administration site conditions (severe AEs with CTCAE grade ≥ 3; includes PT mucositis) as well as febrile neutropenia and thrombocytopenia (each severe AE with CTCAE grade ≥ 3).

For the specific AEs of decreased neutrophil count, neutropenia and lymphopenia (each severe AE with CTCAE grade ≥ 3) and cytokine release syndrome (including serious cytokine release syndrome), Liso-Cel showed a statistically significant disadvantage.

There are no statistically significant differences between the treatment arms for the endpoints of neurological toxicity (including severe neurological toxicity) and severe infections.

For the specific AE of febrile neutropenia (CTCAE grade ≥ 3), there is an effect modification for the sAAIPI characteristic. For patients with sAAIPI 0-1, there is a statistically significant difference in favour of Liso-Cel. For patients with sAAIPI 2-3, there is no statistically significant difference between the study arms. There is also an effect modification for the sex characteristic for the specific AE of thrombocytopenia (CTCAE grade ≥ 3). There was no statistically significant difference between the study arms for male patients, while there was a statistically significant difference in favour of Liso-Cel for female patients. As these effect modifications are not shown for further endpoints, the significance of the available subgroup results for the overall assessment of the additional benefit is considered inadequate.

Conclusion on side effects

In the overall assessment, there are no relevant differences for the benefit assessment in the endpoint category of side effects. In detail, there are advantages and disadvantages for the specific AEs, with the advantages outweighing the disadvantages overall.

Overall assessment

For the benefit assessment of lisocabtagene maraleucel (Liso-Cel), data are available from the open-label, randomised phase III TRANSFORM study on mortality, morbidity, quality of life and side effects compared to induction therapy with R-GDP, R-ICE or R-DHAP followed by high-dose therapy with autologous stem cell transplantation.

However, there were no statistically significant differences between the treatment arms for the overall survival.

In the morbidity endpoint category, there was a statistically significant difference in favour of Liso-Cel for the endpoint "failure of the curative therapeutic approach", which is assessed as a significant improvement. No suitable data are available on symptomatology (assessed using EORTC-QLQ-C30 and FACT-LymS) and health status (assessed using EQ-5D-VAS) due to a high percentage of missing values. This also applies to the data on health-related quality of life (collected using EORTC-QLQ-C30).

With regard to side effects, there were no statistically significant differences for severe AEs, serious AEs and the endpoint of discontinuation due to AEs. In detail, there are both advantages and disadvantages for the specific AEs, with advantages outweighing.

In the overall analysis, the G-BA comes to the conclusion that, mainly due to the clearly positive effect with regard to the avoidance of failure of the curative therapeutic approach for Liso-Cel in the treatment of patients with DLBCL, HGBCL, PMBCL and FL3B, who are eligible for high-dose therapy and relapse within 12 months from completion of, or are refractory to, first-line therapy, there is a considerable additional benefit compared to induction chemotherapy with R-GDP, R-ICE or R-DHAP followed by high-dose therapy with autologous stem cell transplantation.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the ongoing open-label, randomised, phase III TRANSFORM study.

The risk of bias at the study level is rated as low.

The endpoint-specific risk of bias is assessed as low for the endpoints of overall survival and failure of the curative therapeutic approach. With regard to the endpoint "overall survival", however, there are uncertainties due to the existing effect modification according to the age characteristic.

Limitations also arise from the fact that no suitable data are available for the patient-reported endpoints on symptomatology, health status and health-related quality of life.

In the overall assessment of the described limitations, the reliability of data for the additional benefit determined is classified in the hint category.

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

An additional benefit is not proven.

Justification:

In the dossier, the pharmaceutical company does not differentiate between different research questions or patient groups depending on the lymphoma entity or the suitability of the patients for high-dose therapy. The pharmaceutical company presents the results of the two single-arm TRANSCEND-WORLD and PILOT studies on Liso-Cel as additional studies in the dossier, in which patients with DLBCL, HGBCL and FL3B who were not in principle eligible for high-dose therapy were enrolled. However, it does not obtain information on the other studies, nor does it include the results of these studies in its derivation of the additional benefit.

There are therefore no data available for the benefit assessment for this patient group. Irrespective of this, based on the single-arm TRANSCEND-WORLD and PILOT studies, no comparison with the appropriate comparator therapy is possible.

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

An additional benefit is not proven.

Justification:

In the dossier, the pharmaceutical company does not differentiate between different research questions or patient groups depending on the lymphoma entity or the suitability of the patients for high-dose therapy. The pharmaceutical company presents the results of the two single-arm TRANSCEND-WORLD and PILOT studies on Liso-Cel as additional studies in the dossier, in which patients ineligible for high-dose therapy were enrolled in principle. However, according to the inclusion criteria of these studies, patients with PMBCL were not enrolled.

The pharmaceutical company does not gather information on the other studies, nor does it include the results of these studies in its derivation of the additional benefit.

There are therefore no data available for the benefit assessment for this patient group. Irrespective of this, based on the single-arm TRANSCEND-WORLD and PILOT studies, no comparison with the appropriate comparator therapy is possible.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient lisocabtagene maraleucel (Liso-Cel).

The therapeutic indication assessed here is as follows: "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."

In the therapeutic indication under consideration, three patient groups were differentiated, with patients in each patient group relapsing within 12 months from completion of, or are refractory to, first-line therapy:

a) Adults with DLBCL, HGBCL, PMBCL and FL3B who are eligible for high-dose therapy

Data from the phase III TRANSFORM study comparing Liso-Cel with induction therapy (R-GDP, R-ICE, R-DHAP) + HDT + autologous SCT are available for these patient groups.

There is no statistically significant difference for the overall survival.

For the endpoint "failure of the curative therapeutic approach", there is a statistically significant difference in favour of Liso-Cel, which is evaluated as a significant improvement.

No suitable data are available on symptomatology (EORTC-QLQ-C30, FACT-LymS), health status (EQ-5D-VAS) and health-related quality of life (EORTC-QLQ-C30).

With regard to side effects, there were no statistically significant differences for severe AEs, serious AEs and the endpoint of discontinuation due to AEs. In detail, there are both advantages and disadvantages for the specific AEs, with advantages outweighing.

Overall, the G-BA identifies a considerable additional benefit of Liso-Cel, mainly due to the clearly positive effect with regard to avoiding the failure of the curative therapeutic approach.

Uncertainties remain in particular due to effect modification for the endpoint of overall survival and the lack of suitable data on patient-reported endpoints on morbidity and quality of life. The reliability of data of the additional benefit identified is therefore classified in the hint category.

b1) Adults with DLBCL, HGBCL and FL3B who are ineligible for high-dose therapy

The research question of adults with DLBCL, HGBCL and FL3B who are ineligible for high-dose therapy was not addressed by the pharmaceutical company in the dossier. Thus, no data are available. An additional benefit is therefore not proven.

b2) Adults with PMBCL who are ineligible for high-dose therapy

The research question of adults with PMBCL who are ineligible for high-dose therapy was not addressed by the pharmaceutical company in the dossier. Thus, no data are available. An additional benefit is therefore not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the information on the patient numbers from the dossier assessment of IQWiG.[14]

The pharmaceutical company does not differentiate between different research questions or patient groups depending on the suitability of the patients for high-dose therapy or the lymphoma entity.

According to IQWiG's statements, the following case numbers result for the individual lymphoma entities based on the calculation steps performed by the pharmaceutical company in the dossier:

- DLBCL and HGBL: approx. 1,605 – 2,260 patients
- FL3B: approx. 31 – 44 patients
- PMBCL: approx. 34 to 49 patients

These case numbers are subject to uncertainties due to the following aspects in the pharmaceutical company's calculation:

The estimate of DLBCL incidence used by the pharmaceutical company is based on data from the preliminary procedure of lisocabtagene maraleucel in third-line therapy.[15] Based on more recent case numbers, the figures are somewhat higher than assumed here. Due to the increasingly differentiated diagnosis and coding of DLBCL, the assumed average rate of increase of the pharmaceutical company may also be overestimated. There are also uncertainties, as HGBCL is listed separately in the newer WHO classifications[10] but the pharmaceutical company considers it to be subsumed under the ICD code of DLBCL.

It is not clear from the sources provided by the pharmaceutical company on which data the information on the rate of relapses and refractory diseases is based. The pharmaceutical company assumes 30% to 40% of patients with relapse or refractoriness to first-line therapy. However, the publication referred to by the pharmaceutical company states a 30% to 40% for relapses and an additional 10% for refractory diseases, which is in favour of a higher upper limit.

[14] Lisocabtagene maraleucel (DLBCL, HGBL, PMBCL and FL3B, second line); A23-48, 30.08.2023

With regard to the calculation of the percentage of patients with relapse within 12 months or primary refractoriness, it remains unclear in two of the sources used by the pharmaceutical company on which data the derived percentage range is based. The upper limit of the percentage range is based on an expert opinion in which it remains unclear whether the occurrence of refractory disease should also be taken into account. The lower limit of the percentage range is based on the ORCHARRD study, in which only patients eligible for high-dose therapy were enrolled. It is therefore unclear whether this percentage also applies to patients who are ineligible for high-dose therapy.

Breakdown of patient numbers according to the present research questions

For the allocation of the patient numbers according to the present research questions, the percentage of patients eligible for high-dose therapy 50%, used in the dossier procedure for lisocabtagene maraleucel in the third line of therapy, is taken as a basis.[15] On the basis of the publications referred to by the pharmaceutical company in this procedure, it remained unclear on which specific data the percentage information was based. However, a percentage of 50% for high-dose capability appears to be widespread in the literature. This results in the following patient numbers for the relevant research questions:

- DLBCL, HGBCL, PMBCL, FL3B, high-dose therapy is an option:
  approx. 835 – 1,180 patients
- DLBCL, HGBCL, FL3B, high-dose therapy is not an option:
  approx. 820 – 1,150 patients
- PMBCL, high-dose therapy is not an option:
  approx. 20 - 25 patients

The patient numbers determined in this procedure are subject to uncertainties and may represent an overestimation or underestimation.

2.3 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

[15] Lisocabtagene maraleucel (DLBCL, PMBCL, FL3B); A22-90, 12.01.2023

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.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 November 2023).

For the presentation of the costs, one year is assumed for all medicinal products.

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

Lisocabtagene maraleucel

Lisocabtagene maraleucel concerns genetically modified, patient's own (autologous) T cells, which are usually obtained by leukapheresis. Since leukapheresis is part of the manufacture of the medicinal product according to Section 4, paragraph 14 Medicinal Products Act, no further costs are incurred in this respect.

Lisocabtagene maraleucel is listed on LAUER-TAXE®, but is only dispensed to appropriately qualified inpatient treatment centres. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic pack, in deviation from the LAUER-TAXE® data usually taken into account.

Lisocabtagene maraleucel is administered as a single intravenous infusion according to the requirements in the underlying product information.

Induction chemotherapy before stem cell transplantation

The induction chemotherapies R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin), R-ICE (rituximab + ifosfamide + carboplatin + etoposide) and R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin) do not have a marketing authorisation in the present therapeutic indication. In accordance with the recommendation of the S3 guideline, the G-BA uses 2 - 3 cycles as the basis for calculating costs in the context of off-label use of these combination therapies[3]. Furthermore, for the treatment regimens and dosages in relation to the combination therapy R-GDP, the study by Crump et al. (2014)[8] referenced in the S3 guideline and, in relation to the combination therapies R-ICE and R-DHAP, the study by Gisselbrecht et al. referenced in the S3 guideline (2010)[16] are taken into account.

Pembrolizumab as monotherapy and nivolumab in combination with brentuximab vedotin

There is no marketing authorisation for pembrolizumab as monotherapy and nivolumab in combination with brentuximab vedotin in this therapeutic indication. The G-BA's cost calculations for the off-label use of these therapies are based on the treatment regimens of the studies referenced in the S3 guideline on pembrolizumab by Zinzani et al. (2017)[12] and on nivolumab in combination with brentuximab vedotin by Zinzani et al. (2019)[13] as well as the study by Armand et al. (2019)[11] on pembrolizumab monotherapy.

Inpatient treatments

Some treatment options of the appropriate comparator therapy are carried out on an inpatient basis. The inpatient costs are calculated on the basis of the case flat fee revenues, which result from the valuation ratios of the respective DRG (Diagnosis Related Group) multiplied by the federal base rate value of 2023 (€ 4,000.71). Furthermore, the nursing revenue is included in the inpatient costs. This is calculated from the average length of stay of the concerned DRG multiplied by the nursing fee according to Section 15 para. 2a KHEntgG (Act on Fees for Full and Semi-inpatient Hospital Services) (from 1 January 2023: € 230) and the treatment-specific nursing revenue valuation ratio.

Treatment period:

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

[16] Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28 (27):4184-90

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Lisocabtagene maraleucel	Single dose	1	1	1
Appropriate comparator therapy				
Induction chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation if there is a response to induction chemotherapy				
Induction chemotherapy				
R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin)[8]				
Rituximab	1 x per 21-day cycle (day 1)	2 - 3	1	2 - 3
Gemcitabine	2 x per 21-day cycle (day 1 + 8)	2 - 3	2	4 - 6
Dexamethasone	4 x per 21-day cycle (day 1 - 4)	2 - 3	4	8 - 12
Cisplatin	1 x per 21-day cycle (day 1)	2 - 3	1	2 - 3
R-ICE (rituximab + ifosfamide + carboplatin + etoposide)[16]				
Rituximab	1 x per 21-day cycle (day 1, additionally once on the day before the first cycle)	2 - 3	1	3 - 4
Ifosfamide	1 x per 21-day cycle (day 2)	2 - 3	1	2 - 3
Carboplatin	1 x per 21-day cycle (day 2)	2 - 3	1	2 - 3
Etoposide	3 x per 21-day cycle (day 1 - 3)	2 - 3	3	6 - 9
R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin)[8,16]				
Rituximab	1 x per 21-day cycle (day 1;	2 - 3	1	2 - 4

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	additionally once **optionally** on the day before the first cycle)			
Dexamethasone	4 x per 21-day cycle (day 1 - 4)	2 - 3	4	8 - 12
Cytarabine	2 x on day 2 of a 21-day cycle	2 - 3	1	2 - 3
Cisplatin	1 x per 21-day cycle (day 1)	2 - 3	1	2 - 3
High-dose chemotherapy with autologous stem cell transplantation				
Stem cell collection from autologous donors with chemotherapy or with most severe complications or comorbidities (CC), age > 15 years	once		15.9 (average length of stay)	15.9
Autologous stem cell transfusion	once		23.4 (average length of stay)	23.4
Induction chemotherapy followed by high-dose chemotherapy with allogeneic stem cell transplantation if there is a response to induction chemotherapy				
Induction therapy				
R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin)[8]				
Rituximab	1 x per 21-day cycle (day 1)	2 - 3	1	2 - 3
Gemcitabine	2 x per 21-day cycle (day 1 + 8)	2 - 3	2	4 - 6
Dexamethasone	4 x per 21-day cycle (day 1 - 4)	2 - 3	4	8 - 12
Cisplatin	1 x per 21-day cycle (day 1)	2 - 3	1	2 - 3

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
R-ICE (rituximab + ifosfamide + carboplatin + etoposide)[Fehler! Textmarke nicht definiert.]				
Rituximab	1 x per 21-day cycle (day 1; additionally once on the day before the first cycle)	2 - 3	1	3 - 4
Ifosfamide	1 x per 21-day cycle (day 2)	2 - 3	1	2 - 3
Carboplatin	1 x per 21-day cycle (day 2)	2 - 3	1	2 - 3
Etoposide	3 x per 21-day cycle (day 1 - 3)	2 - 3	3	6 - 9
R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin)[8,16]				
Rituximab	1 x per 21-day cycle (day 1; additionally once **optionally** on the day before the first cycle)	2 - 3	1	2 - 4
Dexamethasone	4 x per 21-day cycle (day 1 - 4)	2 - 3	4	8 - 12
Cytarabine	2 x on day 2 of a 21-day cycle	2 - 3	1	2 - 3
Cisplatin	1 x per 21-day cycle (day 1)	2 - 3	1	2 - 3
High-dose chemotherapy with allogeneic stem cell transplantation				
Highly complex and intensive block chemotherapy	once		7.5 (average length of stay)	7.5
Allogeneic stem cell transfusion	once		35.0 (average length of stay)	35.0

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Lisocabtagene maraleucel	Single dose	1	1	1
Appropriate comparator therapy				
Polatuzumab vedotin + bendamustine + rituximab				
Polatuzumab vedotin	1 x per 21-day cycle	6.0	1	6.0
Bendamustine	2 x per 21-day cycle	6.0	2	12.0
Rituximab	1 x per 21-day cycle	6.0	1	6.0
Tafasitamab + lenalidomide				
Tafasitamab	Cycle 1: Day 1, 4, 8, 15 and 22 (28-day cycle)	13.0	Cycle 1: 5	33.0
	Cycle 2 + 3: Day 1, 8, 15, 22 (28-day cycle)		Cycle 2 + 3: 4	
	Cycle 4 up to disease progression: Day 1 and 15 (28-day cycle)		From cycle 4 onwards: 2	
Lenalidomide	Day 1 – 21 of a 28-day cycle	12.0	21	252.0

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	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Lisocabtagene maraleucel	Single dose	1	1	1
Appropriate comparator therapy				
Pembrolizumab monotherapy[11,12]				
Pembrolizumab	1 x per 21-day cycle (Day 1)	17.4	1	17.4
Nivolumab + brentuximab vedotin[13]				
Nivolumab	1 x per 21-day cycle (1st cycle: Day 8; from 2nd cycle: Day 1)	17.4	1	17.4
Brentuximab vedotin	1 x per 21-day cycle (Day 1)	17.4	1	17.4

Consumption:

For dosages depending on body weight or body surface, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).[17]

The consumption of vials and infusion bags is presented for the medicinal product to be assessed, lisocabtagene maraleucel, according to the requirements in the product information. These are administered to the patient in a single infusion depending on the number of cells per vial or infusion bag. The annual treatment costs of lisocabtagene maraleucel are independent of the specific number of vials or infusion bags used.

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

[17] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Lisocabtagene maraleucel	100×10^6 viable CAR+ T cells	100×10^6 viable CAR+ T cells	1 single infusion bag	1	1 single infusion bag
Appropriate comparator therapy					
Induction chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation if there is a response to induction chemotherapy					
Induction chemotherapy					
R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin)[8]					
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	2 - 3	2.0 x 500 mg + 6.0 x 100 mg – 3.0 x 500 mg + 9.0 x 100 mg
Gemcitabine	1,000 mg/m² = 1,900 mg	1,900 mg	1 x 2,000 mg	4 - 6	4.0 x 2,000 mg – 6.0 x 2,000 mg
Dexa-methasone	40 mg	40 mg	1 x 40 mg	8 - 12	8.0 x 40 mg – 12.0 x 40 mg
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 100 mg + 1 x 50 mg	2 - 3	2.0 x 100 mg + 2.0 x 50 mg – 3.0 x 100 mg + 3.0 x 50 mg
R-ICE (rituximab + ifosfamide + carboplatin + etoposide)[Fehler! Textmarke nicht definiert.]					
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	3 - 4	3.0 x 500 mg + 9.0 x 100 mg – 4.0 x 500 mg + 12.0 x 100 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Ifosfamide	5,000 mg/m² = 9,500 mg	9,500 mg	2 x 5000 mg	2 - 3	4.0 x 5000 mg – 6.0 x 5000 mg
Carboplatin	AUC = 5 (= 641.4 mg); max. 800 mg	641.4 mg – 800 mg	1 x 600 mg + 1 x 50 mg – 1 x 600 mg + 4 x 50 mg	2 - 3	2.0 x 600 mg + 2.0 x 50 mg - 3.0 x 600 mg + 3.0 x 50 mg – 2.0 x 600 mg + 8.0 x 50 mg - 3.0 x 600 mg + 12.0 x 50 mg
Etoposide	100 mg/m² = 190 mg	190 mg	1 x 200 mg	6 - 9	6.0 x 200 mg – 9.0 x 200 mg
R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin)[8,16]					
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	2 - 4	2.0 x 500 mg + 6.0 x 100 mg – 4.0 x 500 mg + 12.0 x 100 mg
Dexa-methasone	40 mg	40 mg	1 x 40 mg	8 - 12	8.0 x 40 mg – 12.0 x 40 mg
Cytarabine	2 x daily 2,000 mg/m² = 2 x 3,800 mg	7,600 mg	4 x 2,000 mg	2 - 3	8.0 x 2,000 mg – 12.0 x 2,000 mg
Cisplatin	100 mg/m² = 190 mg	190 mg	2 x 100 mg	2 - 3	4.0 x 100 mg – 6.0 x 100 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Induction chemotherapy followed by high-dose chemotherapy with allogeneic stem cell transplantation if there is a response to induction chemotherapy					
Induction therapy					
R-GDP (rituximab + gemcitabine + dexamethasone + cisplatin)[8]					
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	2 - 3	2.0 x 500 mg + 6.0 x 100 mg – 3.0 x 500 mg + 9.0 x 100 mg
Gemcitabine	1,000 mg/m² = 1,900 mg	1,900 mg	1 x 2,000 mg	4 - 6	4.0 x 2,000 mg – 6.0 x 2,000 mg
Dexa-methasone	40 mg	40 mg	1 x 40 mg	8 - 12	8.0 x 40 mg – 12.0 x 40 mg
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 100 mg + 1 x 50 mg	2 - 3	2.0 x 100 mg + 2.0 x 50 mg – 3.0 x 100 mg + 3.0 x 50 mg
R-ICE (rituximab + ifosfamide + carboplatin + etoposide)[Fehler! Textmarke nicht definiert.]					
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	3 - 4	3.0 x 500 mg + 9.0 x 100 mg – 4.0 x 500 mg + 12.0 x 100 mg
Ifosfamide	5,000 mg/m² = 9,500 mg	9,500 mg	2 x 5000 mg	2 - 3	4.0 x 5000 mg – 6.0 x 5000 mg
Carboplatin	AUC = 5 (= 641.4 mg); max. 800 mg	641.4 mg – 800 mg	1 x 600 mg + 1 x 50 mg – 1 x 600 mg + 4 x 50 mg	2 - 3	2.0 x 600 mg + 2.0 x 50 mg - 3.0 x 600 mg + 3.0 x 50 mg – 2.0 x 600 mg + 8.0 x 50 mg - 3.0 x 600 mg + 12.0 x 50 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Etoposide	100 mg/m² = 190 mg	190 mg	1 x 200 mg	6 - 9	6.0 x 200 mg – 9.0 x 200 mg
R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin)[8,16]					
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	2 - 4	2.0 x 500 mg + 6.0 x 100 mg – 4.0 x 500 mg + 12.0 x 100 mg
Dexa-methasone	40 mg	40 mg	1 x 40 mg	8 - 12	8.0 x 40 mg – 12.0 x 40 mg
Cytarabine	2 x daily 2,000 mg/m² = 2 x 3,800 mg	7,600 mg	4 x 2,000 mg	2 - 3	8.0 x 2,000 mg – 12.0 x 2,000 mg
Cisplatin	100 mg/m² = 190 mg	190 mg	2 x 100 mg	2 - 3	4.0 x 100 mg – 6.0 x 100 mg

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Lisocabtagene maraleucel	100×10^6 viable CAR+ T cells	100×10^6 viable CAR+ T cells	1 single infusion bag	1	1 single infusion bag

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Polatuzumab vedotin + bendamustine + rituximab					
Polatuzumab vedotin	1.8 mg/kg = 138.6 mg	138.6 mg	1 x 140 mg	6.0	6.0 x 140 mg
Bendamustine	90 mg/m^2 = 171 mg	171 mg	1 x 100 mg + 3 x 25 mg	12.0	12.0 x 100 mg + 36.0 x 25 mg
Rituximab	375 mg/m^2 = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	6.0	6.0 x 500 mg + 18.0 x 100 mg
Tafasitamab + lenalidomide					
Tafasitamab	12 mg/kg = 924 mg	924 mg	5 x 200 mg	33.0	165.0 x 200 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	252.0	252.0 x 25 mg

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	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Lisocabtagene maraleucel	100 × 10^6 viable CAR+ T cells	100 × 10^6 viable CAR+ T cells	1 single infusion bag	1	1 single infusion bag
Appropriate comparator therapy					
Pembrolizumab monotherapy[11,12]					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
Nivolumab + brentuximab vedotin[13]					
Nivolumab	240 mg	240 mg	2 x 120 mg	17.4	34.8 x 120 mg
Brentuximab vedotin	1.8 mg/kg = 138.6 mg	138.6 mg	3 x 50 mg	17.4	52.2 x 50 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates

in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Inpatient treatments:

Calculation year	DRG	Average length of stay [d]	DRG valuation ratio (main department)	Federal base case value	Nursing revenue valuation ratio	Nursing fee	Case flat fee revenue	Nursing revenue	Total case flat fee revenue and nursing revenue
Appropriate comparator therapy									
High-dose chemotherapy with allogeneic stem cell transplantation									
2023	R61G	7.5	0.992	€ 4,000.71	0.7667	€ 230	€ 3,968.70	€ 1,323.56	€ 5,291.26
2023	A04E	35.0	9.226	€ 4,000.71	1.9083	€ 230	€ 36,910.55	€ 15,362.82	€ 52,272.37
High-dose chemotherapy with autologous stem cell transplantation									
2023	A42A	15.9	1.979	€ 4,000.71	0.7723	€ 230	€ 7,917.41	€ 2,824.30	€ 10,741.71
2023	A15C	23.4	5.380	€ 4,000.71	1.2260	€ 230	€ 21,523.82	€ 6,598.33	€ 28,122.15

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (purchase price clinic pack plus value added tax)	Value added tax (19%)	Costs of the medicinal product
Medicinal product to be assessed				
Lisocabtagene maraleucel	1 single infusion bag	€ 345,000	€ 0[18]	€ 345,000

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Appropriate comparator therapy					
Rituximab					
Rituximab 500 mg	2 CIS	€ 3,639.53	€ 2.00	€ 350.68	€ 3,286.85
Rituximab 500 mg	1 CIS	€ 1,819.93	€ 2.00	€ 172.53	€ 1,645.40
Rituximab 100 mg	2 CIS	€ 748.12	€ 2.00	€ 69.93	€ 676.19

[18] The medicinal product is exempt from VAT at the applied LAUER-TAXE® last revised.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Gemcitabine					
Gemcitabine 2,000 mg	1 CIS	€ 194.23	€ 2.00	€ 8.68	€ 183.55
Dexamethasone					
Dexamethasone 40 mg	10 TAB	€ 46.29	€ 2.00	€ 0	€ 44.29
Dexamethasone 40 mg	20 TAB	€ 81.59	€ 2.00	€ 0	€ 79.59
Cisplatin 142.5 mg					
Cisplatin 100 mg	1 CIS	€ 84.13	€ 2.00	€ 9.22	€ 72.91
Cisplatin 50 mg	1 CIS	€ 47.73	€ 2.00	€ 4.61	€ 41.12
Cisplatin 190 mg					
Cisplatin 100 mg	1 CIS	€ 76.59	€ 2.00	€ 3.10	€ 71.49
Ifosfamide					
Ifosfamide 5 g	1 CIS	€ 177.77	€ 2.00	€ 7.90	€ 167.87
Carboplatin					
Carboplatin 600 mg	1 CIS	€ 300.84	€ 2.00	€ 13.74	€ 285.10
Carboplatin 50 mg	1 CIS	€ 34.66	€ 2.00	€ 1.11	€ 31.55
Etoposide					
Etoposide 200 mg	1 CIS	€ 81.90	€ 2.00	€ 3.35	€ 76.55
Cytarabine					
Cytarabine 2,000 mg	1 ILL	€ 77.06	€ 2.00	€ 3.12	€ 71.94
Bendamustine					
Bendamustine 25 mg	5 PCI	€ 414.43	€ 2.00	€ 51.01	€ 361.42
Bendamustine 25 mg	1 PCI	€ 99.39	€ 2.00	€ 11.15	€ 86.24
Bendamustine 100 mg	5 PCI	€ 1,620.96	€ 2.00	€ 204.07	€ 1,414.89
Bendamustine 100 mg	1 PCI	€ 331.03	€ 2.00	€ 40.46	€ 288.57
Other medicinal products					
Polatuzumab vedotin 140 mg	1 PIC	€ 10,680.39	€ 2.00	€ 433.33	€ 10,245.06
Tafasitamab 500 mg	1 PCI	€ 654.48	€ 2.00	€ 61.05	€ 591.43
Lenalidomide 25 mg	63 HC	€ 117.32	€ 2.00	€ 8.38	€ 106.94
Nivolumab 120 mg	1 CIS	€ 1,546.96	€ 2.00	€ 145.81	€ 1,399.15
Brentuximab vedotin 50 mg	1 PIC	€ 3,378.54	€ 2.00	€ 325.13	€ 3,051.41
Pembrolizumab 100 mg	1 CIS	€ 2,974.82	€ 2.00	€ 285.60	€ 2,687.22

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Abbreviations: HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; CAP = capsules; PIC = powder for the preparation of an infusion solution concentrate; PCI = powder for a concentrate for the preparation of an infusion solution; ILL = injection/infusion solution					

LAUER-TAXE® last revised: 1 November 2023

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

Prophylactic premedication

Antipyretic and antihistamine premedication is only recommended in the product information of lisocabtagene maraleucel. These costs cannot be quantified as no specific dosage recommendations are given in the product information of polatuzumab vedotin.

Mesna is given in combination with ifosfamide for the prophylaxis of haemorrhagic cystitis.

Conditioning chemotherapy for lymphocyte depletion under CAR-T cell therapy

Lisocabtagene maraleucel is an autologous cell product produced from the patient's own T cells. Therefore, a leukapheresis is usually necessary to obtain the cell material. Since leukapheresis is part of the manufacture of the medicinal product pursuant to Section 4, paragraph 14 Medicinal Products Act (AMG), no further costs are incurred in this respect for lisocabtagene maraleucel.

For lisocabtagene maraleucel, a treatment regimen for lymphocyte depletion, consisting of

intravenous administration of cyclophosphamide (500 mg/m^2 = 950 mg) and fludarabine (30 mg/m^2 = 57 mg), is given daily for 3 days, with infusion administered 3 to 5 days after the start of lymphocyte depletion.

Screening for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) under CAR-T cell therapy

Patients should be tested for hepatitis B, hepatitis C and HIV infection prior to starting treatment with lisocabtagene maraleucel. This test is not required for all therapy options of the appropriate comparator therapy. Since there is a regular difference between the medicinal product to be assessed and the appropriate comparator therapy with regard to the tests for hepatitis B, hepatitis C and HIV, the costs of additionally required SHI services are presented in the resolution.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed							
Lisocabtagene maraleucel							
Conditioning chemotherapy for lymphocyte depletion							
Cyclophosphamide 300 mg/m^2 = 570 mg	10 PSI at 200 mg	€ 62.80	€ 2.00	€ 4.89	€ 55.91	3.0	€ 55.91
Fludarabine 30 mg/m^2 = 57 mg	1 CII at 50 mg	€ 118.54	€ 2.00	€ 5.09	€ 111.45	3.0	€ 668.70
Screening for HBV, HCV and HIV							
Hepatitis-B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Hepatitis C HCV antibody status (GOP: 32618)	-	-	-	-	€ 9.80	1.0	€ 9.80

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
HIV HIV-1 and HIV-2 antibody status (GOP: 32575)	-	-	-	-	€ 4.45	1.0	€ 4.45
Appropriate comparator therapy							
Induction chemotherapy (R-GDP, R-DHAP, R-ICE) prior to autologous or allogeneic stem cell transplantation							
Rituximab (R-GDP, R-DHAP, R-ICE)							
HBV diagnostics (R-GDP, R-DHAP, R-ICE)							
HBV test Hepatitis B Surface antigen status (GOP number 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Hepatitis-B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Premedication (R-GDP)							
Dimetindene (1 mg/10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.53	€ 16.19	2.0 – 3.0	€ 16.19 – € 32.38
Paracetamol[19] (500 mg - 1,000 mg, PO)	10 TAB 500 mg – 10 TAB 1,000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	2.0 – 3.0	€ 2.68 – € 3.01
Premedication (R-ICE)							
Dimetindene (1 mg/10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.53	€ 16.19	3.0 – 4.0	€ 32.38
Paracetamol[19] (500 mg - 1,000 mg, PO)	10 TAB 500 mg – 10 TAB 1,000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	3.0 – 4.0	€ 2.68 – € 3.01
Premedication (R-DHAP)							
Dimetindene (1 mg/10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.53	€ 16.19	2.0 – 4.0	€ 16.19 – € 32.38

[19] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Paracetamol[19] (500 mg - 1,000 mg, PO)	10 TAB 500 mg – 10 TAB 1,000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	2.0 – 4.0	€ 2.68 – € 3.01
Cisplatin (R-GDP, R-DHAP)							
Antiemetic treatment: In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	2.0 – 3.0	91.10
Sodium chloride 0.9% infusion solution, 3 l - 4.4 l/day	6 x 1,000 ml INF	€ 25.09	€ 1.25	€ 2.05	€ 21.79	2.0 – 3.0	€ 21.79 – € 54.37
	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58		
Mesna (R-ICE)							
Mesna (Bolus with 1,900 mg mesna (= 20% of the ifosfamide dose), followed by 24-hour continuous infusion with at least 1,900 mg up to 9,500 mg (= 20% - 100% of the ifosfamide dose), followed by subsequent infusion with up to 4,750 mg mesna (= 0% - 50% of the ifosfamide dose) for 6 - 12 hours	Bolus with 1,900 mg followed by 24-hour continuous infusion with 1,900 mg						
	10 SFI 400 mg	€ 32.26	€ 2.00	€ 0.99	€ 29.27	2 - 3	€ 58.54 - € 87.81
	Bolus of 1,900 mg followed by 24-hour continuous infusion of 9,500 mg followed by subsequent infusion of 4,750 mg						
	50 AMP 400 mg	€ 148.19	€ 2.00	€ 17.33	€ 128.86	2-3	€ 257.72 - € 386.58
Polatuzumab vedotin + bendamustine + rituximab							
Bendamustine and rituximab							
HBV diagnostics							
HBV test Hepatitis B surface antigen status (GOP number 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Hepatitis-B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Rituximab							
Premedication							
Dimetindene (1 mg/10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.53	€ 16.19	6.0	€ 48.57
Paracetamol[19] (500 mg - 1,000 mg, PO)	10 TAB at 500 mg – 10 TAB at 1,000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	6.0	€ 2.68 – € 3.01
Abbreviations: SFI = solution for injection; INF = infusion solution; CII = concentrate for injection or infusion solution; TAB = tablets; PSI = powder for solution for injection							

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Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient:

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the

designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGBV.

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.

Justification for the findings on designation in the present 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

- 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.

References:

Product information of lisocabtagene maraleucel (Breyanzi); BREYANZI® 1.1 - 70 × 10^6 cells/ml / 1.1 - 70 × 10^6 cells/ml infusion dispersion; last revised: September 2023

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

- 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.

References:

Product information of lisocabtagene maraleucel (Breyanzi); BREYANZI® 1.1 - 70 × 10^6 cells/ml / 1.1 - 70 × 10^6 cells/ml infusion dispersion; last revised: September 2023

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.

References:

Product information of lisocabtagene maraleucel (Breyanzi); BREYANZI® 1.1 - 70 × 10^6 cells/ml / 1.1 - 70 × 10^6 cells/ml infusion dispersion; last revised: September 2023

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 7 December 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The plenum newly determined the appropriate comparator therapy at its session on 1 June 2023.

On 30 May 2023, the pharmaceutical company submitted a dossier for the benefit assessment of lisocabtagene maraleucel to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 01 June 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient lisocabtagene maraleucel.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 August 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 September 2023. The deadline for submitting written statements was 22 September 2023.

The oral hearing was held on 9 October 2023.

By letter dated 10 October 2023, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 26 October 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 November 2023, and the proposed resolution was approved.

At its session on 16 November 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 December 2021	Determination of the appropriate comparator therapy
Plenum	1 June 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	5 October 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	9 October 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 October 2023 1 November 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	7 November 2023	Concluding discussion of the draft resolution
Plenum	16 November 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 November 2023

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

Prof. Hecken