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) Axicabtagene ciloleucel (reassessment of an orphan drug after exceeding the EUR 30 million turnover limit: diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma, after at least 2 prior therapies)

of 21 December 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 axicabtagene ciloleucel (Yescarta) was listed for the first time on 1 December 2019 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Axicabtagene ciloleucel for the treatment of relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

At its session on 3 November 2022, the G-BA decided on the benefit assessment of axicabtagene ciloleucel in the therapeutic indication "Treatment of adult patients with

relapsed or refractory (r/r) DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy" in accordance with Section 35a SGB V.

Axicabtagene ciloleucel concerns a somatic cell therapy within the meaning of Section 4, paragraph 9 Medicinal Products Act.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of € 30 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Section 5, paragraphs 1 to 6 within three months of being requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

Yescarta exceeded the EUR 30 million turnover limit on 1 December 2022 and has not yet been assessed with evidence of medical benefit and additional medical benefit in relation to the appropriate comparator therapy. By resolution of 2 February 2023 the procedure was suspended till 1 July 2023.

In a letter dated 2 February 2023, the pharmaceutical company was requested to submit evidence in accordance with sentence 3 numbers 2 and 3 by 1 July 2023 because of exceeding the 30 million euro turnover limit, and to provide evidence of the additional benefit in deviation from Section 35a, paragraph 1, sentence 11 SGB V. The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 6 VerfO on 30 June 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 2 October 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 axicabtagene ciloleucel compared to 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. 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 axicabtagene ciloleucel.

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:

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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

2.1.1 Approved therapeutic indication of Axicabtagene ciloleucel (Yescarta) according to the product information

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

Therapeutic indication of the resolution (resolution of 21.12.2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy, who are eligible for CAR-T cell therapy or stem cell transplantation

Appropriate comparator therapy for axicabtagene ciloleucel:

- Tisagenlecleucel (only for subjects with DLBCL)

  or

- Lisocabtagene maraleucel

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 axicabtagene ciloleucel, the following active ingredients are approved for the present therapeutic indication:

Bleomycin, cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, epcoritamab, glofitamab, ifosfamide, loncastuximab tesirine, melphalan, methotrexate, methylprednisolone, mitoxantrone, pixantrone, polatuzumab vedotin, prednisolone, prednisone, tafasitamab, trofosfamide, vinblastine, vincristine, vindesine, rituximab, lisocabtagene maraleucel and tisagenlecleucel.

Some of the medicinal products listed have a marketing authorisation for the superordinate therapeutic indication "non-Hodgkin lymphoma". The marketing authorisations are partly linked to (specified) concomitant active ingredients or do not fully cover the present therapeutic indication.

on 2. In principle, autologous or allogeneic stem cell transplantation can be considered as a non-medicinal treatment for relapsed or refractory DLBCL and PMBCL. 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:

Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Loncastuximab tesirine (resolution of 2 November 2023)

- Lisocabtagene maraleucel (resolution of 6 April 2023)
- Tafasitamab (resolution of 3 March 2022)
- Polatuzumab vedotin (resolution of 20 August 2020)
- Pixantrone (resolution of 16 May 2013)
- Tisagenlecleucel (resolution of 17 September 2020)

Guideline for Inpatient Treatment (last revised 7 December 2022: Allogeneic stem cell transplantation for aggressive B-non-Hodgkin lymphomas):

- 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-cell non-Hodgkin lymphomas 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.

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 care.

Overall, the evidence on treatment options for the present advanced treatment setting of relapsed or refractory DLBCL and PMBCL after at least two lines of therapy is limited. It is clear from the present guidelines and from the statements made by the clinical experts at the oral hearing that the therapy recommendations for subjects with PMBCL who are eligible for CAR T-cell therapy or stem cell transplantation are basically based on those for DLBCL, so that no differentiation of patient groups is made in this respect for the determination of the appropriate comparator therapy.
The present therapeutic indication generally refers to patients with relapsed or refractory (r/r) DLBCL and PMBCL, after two or more lines of systemic therapy, and is not limited in terms of patient eligibility or ineligibility for an intensive therapeutic approach. According to the S3 guideline, there are distinct treatment recommendations for therapy with a primarily curative intention, such as CAR-T cell therapy and stem cell transplantation on the one hand, and therapy with a primarily palliative intention on the other. According to the scientific-medical societies, there is also a corresponding differentiation between curative and non-curative treatment options. In this regard, it also emerged from the statements submitted by clinical experts in the benefit assessment procedure on loncastuximab tesirine (resolution of

2 November 2023) as well as in the present benefit assessment procedure that in clinical practice, not only the suitability for high-dose therapy but also the suitability for CAR-T cell therapy are relevant parameters with regard to the treatment decision from the third line of therapy onwards.

As axicabtagene ciloleucel is a CAR-T cell therapy, it is assumed that patients who are suitable for treatment with axicabtagene ciloleucel are eligible for CAR-T cell therapy or stem cell transplantation. Therefore, patients who are ineligible for CAR-T cell therapy or stem cell transplantation are not taken into account when determining the appropriate comparator therapy.

According to the S3 guideline, CAR-T cell therapy should be carried out from the second relapse onwards if it has not already been carried out in second-line therapy. The CAR-T cell therapies axicabtagene ciloleucel, tisagenlecleucel (only for patients with DLBCL) and lisocabtagene maraleucel are available in this therapeutic indication.

For the benefit assessment according to Section 35a SGB V, a comparison with the active ingredient itself, specifically a comparison of identical therapies, is ruled out regarding the question of the benefit assessment. The subject of the present benefit assessment procedure is the active ingredient axicabtagene ciloleucel, which is therefore excluded from the appropriate comparator therapy. 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.

A hint for a non-quantifiable additional benefit was identified for tisagenlecleucel (resolution of 17 September 2020) within the scope of an orphan drug assessment because the scientific data did not allow quantification. The period of validity of the resolution on tisagenlecleucel was limited until 1 September 2023; the benefit assessment procedure is currently in progress after expiry of the deadline. Tisagenlecleucel is only approved for the treatment of adults with DLBCL in this therapeutic indication and therefore only represents an appropriate comparator therapy for these patients.

Lisocabtagene maraleucel is approved for the treatment of relapsed or refractory (r/r) DLBCL, PMBCL and grade 3B follicular lymphoma, after at least 2 prior therapies. No additional benefit was identified for lisocabtagene maraleucel compared with the appropriate comparator therapy in the benefit assessment by resolution of 6 April 2023, as the data presented did not allow an assessment of the additional benefit. Lisocabtagene maraleucel is recommended by the present guidelines for the treatment of suitable patients with DLBCL and PMBCL after two or more lines of systemic therapy in the same way as the other approved CAR-T cell therapies and is used for the treatment of both DLBCL and PMBCL according to the statements by the clinical experts at the oral hearing. Thus, lisocabtagene maraleucel and tisagenlecleucel (only for subjects with DLBCL) are designated as equally appropriate comparator therapies.

For patients who have already received CAR-T cell therapy or who are unsuitable for such therapy, salvage chemoimmunotherapy including stem cell transplantation (autologous or allogeneic) is the therapy standard according to the present guidelines and the statements of the scientific-medical societies. However, CAR-T cell therapy with axicabtagene ciloleucel is not normally considered for these patients according to the present therapeutic indication, which is why chemoimmunotherapy followed by

autologous or allogeneic stem cell transplantation is not considered as an appropriate comparator therapy for axicabtagene ciloleucel.

The therapy options polatuzumab vedotin in combination with bendamustine and rituximab (Pola-BR), tafasitamab in combination with lenalidomide and pixantrone are mainly suitable for subjects who are unsuitable for CAR-T cell therapy or stem cell transplantation on the basis of the available evidence and according to the statements made by the clinical experts at the oral hearing. Therefore, these therapy options are not determined as appropriate comparator therapies for the subjects eligible for CAR-T cell therapy or stem cell transplantation.

In addition, the active ingredient loncastuximab tesirine was approved on 20 December 2022 for the treatment of relapsed or refractory (r/r) DLBCL and high-grade B-cell lymphoma (HGBL), after two or more lines of systemic treatment. No additional benefit was identified for loncastuximab tesirine compared with the appropriate comparator therapy in the benefit assessment by resolution of 2 November 2023. This therapy option has only been available for a relatively short time and is not recommended by the guidelines and scientific-medical societies for the treatment of patients in this therapeutic indication. Against this background, loncastuximab tesirine is not determined as an appropriate comparator therapy.

It is also assumed that best supportive care alone is not an option for patients who are suitable for CAR-T cell therapy or stem cell transplantation.

The active ingredients glofitamab and epcoritamab are treatment options in the therapeutic indication of relapsed or refractory (r/r) DLBCL, after at least two lines of systemic therapy. These active ingredients were only recently approved (marketing authorisation on 07.07.2023 and 22.09.2023). Based on the generally accepted state of medical knowledge, glofitamab and epcoritamab are not determined to be an appropriate comparator therapy for the present resolution.

Overall, CAR-T cell therapy with tisagenlecleucel (only for subjects with DLBCL) or lisocabtagene maraleucel is therefore determined to be an appropriate comparator therapy.

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

Originally, the appropriate comparator therapy was determined as follows:

a) Adults with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy, who are eligible for a high-dose therapy

Appropriate comparator therapy for axicabtagene ciloleucel

Therapy according to doctor's instructions under consideration of

- Tisagenlecleucel (only for subjects with DLBCL),
- induction therapy with MINE (mesna, ifosfamide, mitoxantrone, etoposide) followed by high-dose therapy with **autologous** stem cell transplantation if there is a response to induction therapy

  and

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

b) Adults with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy, who are ineligible for a high-dose therapy

Appropriate comparator therapy for axicabtagene ciloleucel

Therapy according to doctor's instructions under consideration of

- CEOP (cyclophosphamide, etoposide, vincristine, prednisone),
- dose-adjusted EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone),
- polatuzumab vedotin + bendamustine + rituximab (only for subjects with DLBCL),
- tafasitamab + lenalidomide (only for subjects with DLBCL),
- pixantrone monotherapy,
- radiation,
- and best supportive care.

This appropriate comparator therapy was determined for the present benefit assessment procedure on axicabtagene ciloleucel 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 relapsed or refractory DLBCL and PMBCL after two or more lines of systemic therapy are mentioned in the present 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 axicabtagene ciloleucel, 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 addition, the statements submitted by clinical experts in the benefit assessment procedure for loncastuximab tesirine for the treatment of DLBCL and high-grade B-cell lymphoma (HGBL) after at least two prior therapies (resolution of 2 November 2023) and also in the present benefit assessment procedure showed that, with regard to the treatment decision from the third line of therapy onwards, not only the suitability for high-dose therapy but also the suitability for CAR-T cell therapy are relevant parameters; in this respect, according to the S3 guideline, there are distinct treatment recommendations for therapy with a primarily curative intention, such as CAR-T cell therapy and stem cell transplantation on the one hand, and therapy with a primarily palliative intention on the other.

Against this background, the appropriate comparator therapy was changed for the present resolution.

As a result of this change in the appropriate comparator therapy, tisagenlecleucel (only for subjects with DLBCL) or lisocabtagene maraleucel are determined as the appropriate comparator therapy for axicabtagene ciloleucel. Therefore, the resolution is limited in time. The time limit enables the pharmaceutical company to submit suitable evaluations that correspond to the appropriate comparator therapy determined by the present resolution.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of axicabtagene ciloleucel is assessed as follows:

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of axicabtagene ciloleucel in patients with relapsed/refractory (r/r) DLBCL and PMBCL, the pharmaceutical company presented data from the pivotal, single-arm phase I/II ZUMA-1 study, the retrospective Bachy 2022 study as well as a supporting meta-analysis of data from published registry studies and an analysis of data from the EUPAS32539 registry. The studies and analyses submitted by the pharmaceutical company are considered unsuitable for the benefit assessment of axicabtagene ciloleucel.

ZUMA-1 study

The ZUMA-1 study is a single-arm, multicentre phase I/II study to investigate the efficacy and safety of axicabtagene ciloleucel in subjects with relapsed or refractory (r/r) DLBCL (including the transformed follicular lymphoma subtype) and primary mediastinal large B-cell lymphoma (PMBCL).

The ZUMA-1 study was conducted from April 2015 to July 2023 in a total of 24 study sites across North America (23) and Israel (1).

Study participants had to have chemorefractory disease according to the criteria defined in the study. In addition, they had to have received prior therapy with an anti-CD20 antibody as well as anthracycline-based chemotherapy.

The study included six cohorts, of which only those subjects included in cohorts 1 and 2 were treated according to the product information. A total of 111 patients were enrolled in phase II of the ZUMA-1 study, depending on their disease entity. Of these, 81 subjects with DLBCL were assigned to cohort 1. Cohort 2 enrolled 21 subjects with TFL and 9 subjects with PMBCL. A total of 101 patients actually received axicabtagene ciloleucel treatment (cohort 1: n = 77, cohort 2: n = 24).

The period from the time of enrolment in the study, which corresponds to the time of leukapheresis, to infusion of axicabtagene ciloleucel was 23 days. Bridge therapy was not allowed in this period.

Axicabtagene ciloleucel was administered as a single infusion. Concomitant medications allowed in case of cytokine release syndrome (CRS) or neurologic events were tocilizumab, corticosteroids and other immunosuppressants (CRS only). Post-treatment follow-up was planned between study week 2 and study month 3, after which long-term follow-up was planned until month 24, followed by survival follow-up until the end of the study (maximum 15 years).

The primary endpoint of the ZUMA-1 study was the overall response rate (ORR); secondary endpoints included overall survival (OS), progression-free survival (PFS) and adverse events (AEs).

For the benefit assessment of axicabtagene ciloleucel, the pharmaceutical company presented evaluations on overall survival, PFS and response for the data cut-off from 11.08.2018 and additionally for the data cut-off from 11.08.2021. For endpoints of the AEs, only evaluations of the data cut-off from 11.08.2018 were presented.

The ZUMA-1 study is unsuitable for the assessment of the additional benefit of axicabtagene ciloleucel, as it does not allow a comparison with the appropriate comparator therapy.

Bachy 2022 study

The Bachy 2022 study is a retrospective evaluation of data from the French DESCAR-T registry.[2] The aim is to compare the efficacy and safety of axicabtagene ciloleucel with

[2] Bachy E, Le Gouill S, Di Blasi R et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. Nat Med 2022; 28(10): 2145-2154. https://dx.doi.org/10.1038/s41591-022-01969-y

tisagenlecleucel in patients with DLBCL who have received at least two prior lines of systemic therapy.

Patients can be included in the French DESCAR-T registry both retrospectively and prospectively if they are being treated with CAR-T cell therapy or if there is an indication for CAR-T cell therapy. The endpoints assessed are overall survival, response, PFS, health-related quality of life and AEs.

A total of 809 patients who were treated with axicabtagene ciloleucel or tisagenlecleucel between December 2019 and October 2021 and recorded in the DESCAR-T registry were enrolled in the Bachy 2022 study. Of these, 729 patients received CAR-T cell therapy (axicabtagene ciloleucel [n = 452] and tisagenlecleucel [n = 277]). A propensity score matching (PSM)-based analysis included 672 infused patients (axicabtagene ciloleucel [n = 419] and tisagenlecleucel [n = 253]). This resulted in a 1:1 matched population of 418 patients.

The primary endpoint of the Bachy 2022 study was PFS from infusion, secondary endpoints included overall survival from infusion, response and some specific AEs such as haematological toxicity, CRS and immune effector cell-associated neurotoxicity syndrome (ICANS).

In the Bachy 2022 study, results were reported on all endpoints for the propensity score-matched population and additional inverse probability of treatment weighting (IPTW) analyses were conducted for all efficacy endpoints.

The pharmaceutical company presents evaluations from the Bachy 2022 study on the endpoints of overall survival from infusion, PFS from infusion, ORR, duration of response (DOR) and some specific AEs (haematological toxicity, CRS and ICANS) for the matched population. In addition, an evaluation of the overall survival endpoint from the time the CAR-T cells were ordered was presented. The IPTW and complete case analyses shown in the publication by Bachy et al. were not presented[2].

For the following reasons, the Bachy 2022 study is considered unsuitable for the assessment of the additional benefit of axicabtagene ciloleucel:

As the Bachy 2022 study is a non-randomised, retrospective study, it cannot be assumed that the required structural similarity between the treatment arms is guaranteed. Differences with regard to relevant patient characteristics must therefore be equalised using adequate analytical methods in order to avoid distortions. The prerequisite for this is the systematic identification of potential confounders. In the Bachy 2022 study, analyses with propensity score adjustment, taking into account 14 potential confounders submitted by the pharmaceutical company, were carried out to compensate for the structural similarity in question. However, it was not described how the confounders considered were identified, whether the selection of confounders was pre-specified and whether the DESCAR-T registry contained information on all potentially relevant confounders. Documents on study planning and statistical analyses in the form of a study protocol and a statistical analysis plan were also not submitted in the dossier.

In addition, in the Bachy 2022 study, the observation for all endpoints did not take place from the decision in favour of CAR-T cell therapy - as provided for in the DESCAR-T registry protocol - but from the time of infusion of the CAR-T cells. In the Bachy 2022 study, a total of 80 subjects out of 809 patients who were scheduled to receive CAR T-cell therapy did not receive such therapy. The reasons for this were, for example, the progression of the disease or death during the waiting period. This means that the intention-to-treat (ITT) principle is violated in the

evaluations of the Bachy 2022 study. Only for the overall survival endpoint were additional analyses presented from the time of ordering the CAR-T cells, without an effect estimator being reported.

With regard to the endpoint category of side effects, the pharmaceutical company only submitted results on some specific adverse events. A complete benefit-risk assessment based on the results of the Bachy 2022 study is therefore not possible.

In the overall assessment, the Bachy 2022 study is considered unsuitable for the benefit assessment of axicabtagene ciloleucel.

Meta-analysis from published registry data

As supporting evidence, the pharmaceutical company presents a meta-analysis of published registry studies. To this end, it conducted a bibliographic literature search in the Embase and MEDLINE databases and included English-language publications from 2017 onwards on prospective and retrospective observational studies with patients with large B-cell lymphoma (LBCL) treated with CAR-T cells (axicabtagene ciloleucel, tisagenlecleucel or lisocabtagene maraleucel). The studies had either no comparator or CAR-T cells as comparator and had to include results on efficacy and/or safety endpoints.

The pharmaceutical company identified 14 patient cohorts for a comparison of axicabtagene ciloleucel with tisagenlecleucel and only considered the results of some large studies for the meta-analysis.

For a comparison of axicabtagene ciloleucel versus tisagenlecleucel, meta-analytically summarised results from adjusted and unadjusted evaluations were presented for the endpoints of response, overall survival, PFS, CRS and neurotoxicity. These results were then compared descriptively with the results from the respective approval studies ZUMA-1 (axicabtagene ciloleucel) and JULIET (tisagenlecleucel), separately for each of the two active ingredients.

The meta-analysis presented is unsuitable for the benefit assessment of axicabtagene ciloleucel, as only evaluations for patients who actually received a CAR T-cell infusion were presented and the ITT principle was therefore not implemented. In addition, it is unclear whether the study pool is complete due to deficiencies in the procurement of information and there is a lack of detailed information on the included studies. Due to a lack of information, it is still unclear whether all patients enrolled in the included studies are covered by the present therapeutic indication.

As the pharmaceutical company only submitted results on the specific adverse events of CRS and neurotoxicity with regard to the endpoint category of side effects, a complete benefit-risk assessment is not possible based on the results of the meta-analysis presented.

EUPAS32539 study

The EUPAS32539 study is based on data from the European Society for Blood and Marrow Transplantation (EBMT) registry, in which all patients treated with axicabtagene ciloleucel in qualified European study sites are surveyed.

This is a multicentre observational study in patients with relapsed or refractory (r/r) DLBCL or PMBCL, after 2 or more lines of systemic therapy, and follicular lymphoma, after 3 or more lines of systemic therapy. Primary endpoints are the occurrence, type and location of

secondary tumours and specific AEs. Secondary endpoints include overall survival, time to next therapy and time to relapse or progression.

Results from the interim report of the EBMT registry were presented for the benefit assessment of axicabtagene ciloleucel. At the time of data cut-off, 979 patients with DLBCL and PMBCL had received an infusion of axicabtagene ciloleucel, after at least two lines of systemic therapy. The report contains evaluations for 773 patients for whom a follow-up form was available on day 100. For these evaluations, results on the endpoints of response and specific AEs (CRS and neurotoxicity) were presented descriptively.

The results of the EUPAS32539 study are unsuitable for the assessment of the additional benefit of axicabtagene ciloleucel, as they do not allow a comparison with the appropriate comparator therapy. In addition, only subjects who actually received CAR-T cell therapy were enrolled in this study, thus violating the ITT principle. Furthermore, apart from a few specific AEs, no complete collection of AEs was made, which is why a complete benefit-risk assessment based on the EUPAS32539 study is not possible.

Extent and probability of the additional benefit

An additional benefit is not proven.

Overall assessment

For the assessment of the additional benefit of axicabtagene ciloleucel in patients with DLBCL and PMBCL, after at least two lines of systemic therapy, the pharmaceutical company presented data from the pivotal phase I/II ZUMA-1 study and the retrospective Bachy 2022 study. In addition, a meta-analysis of published registry data and the EUPAS32539 registry study were presented.

The data presented are unsuitable for the benefit assessment of axicabtagene ciloleucel.

The single-arm ZUMA-1 study does not allow a comparison with the appropriate comparator therapy.

The Bachy 2022 study is unsuitable for the benefit assessment of axicabtagene ciloleucel due to questionable structural similarity between the treatment arms and a lack of systematic identification of potential confounders as well as a violation of the ITT principle. In addition, only results on some specific adverse events were presented, which is why a complete benefit-risk assessment based on the results of the Bachy 2022 study is not possible.

The meta-analysis presented is also unsuitable for the benefit assessment, as the ITT principle was not implemented and relevant information on the studies considered and the patients enrolled is missing. In addition, only results on some specific adverse events were presented, which is why a complete benefit-risk assessment based on the results of the meta-analysis presented is also not possible.

In the EUPAS32539 study, no comparison was made with the appropriate comparator therapy and the ITT principle was also not implemented. In addition, there was no complete collection of AEs, which is why a complete benefit-risk assessment based on this study is not possible. This study is therefore also unsuitable for the benefit assessment of axicabtagene ciloleucel.

Therefore, an additional benefit of axicabtagene ciloleucel in adults with r/r DLBCL and PMBCL after two or more lines of systemic therapy is not proven.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of axicabtagene ciloleucel finds its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by the below-mentioned objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

Due to the present change in the appropriate comparator therapy, the G-BA considers it appropriate to limit the resolution on the additional benefit of axicabtagene ciloleucel. The limitation enables the pharmaceutical company to submit suitable evaluations, which correspond to the appropriate comparator therapy determined by the present resolution, in a new dossier in a timely manner. For this purpose, a limitation of the period of validity of the resolution to 6 months is considered to be appropriate.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 number 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment of the medicinal product with the active ingredient axicabtagene ciloleucel recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of axicabtagene ciloleucel (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that an additional benefit is considered as being not proven. The possibility that a benefit assessment for the medicinal product with the active ingredient axicabtagene ciloleucel can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, nos. 2 – 4 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient axicabtagene ciloleucel (Yescarta) due to the exceeding of the EUR 30 million turnover limit. Axicabtagene ciloleucel was approved as an orphan drug.

The therapeutic indication assessed here is: “treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.”

As axicabtagene ciloleucel is a CAR-T cell therapy, the present assessment refers to patients with relapsed/refractory DLBCL and PMBCL, after two or more lines of systemic therapy who are eligible for CAR-T cell therapy or stem cell transplantation.

For these patients, tisagenlecleucel (only for subjects with DLBCL) or lisocabtagene maraleucel were determined to be an appropriate comparator therapy.

To demonstrate the additional benefit of axicabtagene ciloleucel, the pharmaceutical company presented data from the single-arm phase I/II ZUMA-1 study and the retrospective Bachy 2022 study, as well as a meta-analysis of published registry data and the EUPAS32539 study.

The data presented are unsuitable for the benefit assessment of axicabtagene ciloleucel. The ZUMA-1 and EUPAS32539 studies do not allow a comparison with the appropriate comparator

therapy. The ITT principle was not implemented in the Bachy 2022 and EUPAS32539 studies or in the meta-analysis of published registry data.

In addition, the Bachy 2022 and EUPAS32539 studies and the meta-analysis only presented results on some specific adverse events, which is why a complete benefit-risk assessment based on these data is not possible.

An additional benefit of axicabtagene ciloleucel in adults with relapsed or refractory (r/r) DLBCL and PMBCL, after two or more lines of systemic therapy compared with the appropriate comparator therapy is therefore not proven.

The period of validity of the resolution is limited to 1 July 2024.

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 resolution is based on the information on patient group a) from the resolution on the benefit assessment of loncastuximab tesirine for the treatment of DLBCL and HGBL(resolution of 2 November 2023). This patient group differs from the patient population presented here in that patients with HGBL are also included, while patients with PMBCL are not. The resolution on loncastuximab tesirine was based on the information from the pharmaceutical company's written statement, in which patients with HGBL were not taken into account. Patients with PMBCL were also not included, which results in uncertainties for the present resolution.

Further uncertainties regarding the lower limit arise from the fact that the data originate from a review addressing second-line therapy, i.e. a previous line of therapy. The upper limit was based on data on patient access to CAR-T cell therapies in Austria. This percentage may be an underestimate as correspondingly higher percentages were calculated for Germany.

Despite the uncertainties mentioned, these patient numbers are considered to be more accurate than the data from the pharmaceutical company's dossier, as they relate to the patient population relevant for the benefit assessment of axicabtagene ciloleucel, which is eligible for CAR-T cell therapy or stem cell transplantation.

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 Yescarta (active ingredient: axicabtagene ciloleucel) at the following publicly accessible link (last access: 4 October 2023):

https://www.ema.europa.eu/en/documents/product-information/yescarta-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 axicabtagene ciloleucel 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 axicabtagene ciloleucel and to carry the patient emergency card at all times.

Axicabtagene ciloleucel must be used in a qualified treatment facility. For the infusion of axicabtagene ciloleucel in the present therapeutic indication, the quality assurance measures for the use of CAR-T cells in B-cell neoplasms apply (ATMP Quality Assurance Guideline, Annex 1).

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 December 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.

CAR-T cell therapies

Axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel are 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 for these active ingredients.

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

Axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel are administered as a single intravenous infusion according to the requirements in the underlying product information.

Treatment period:

Adults with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy, who are eligible for CAR-T cell therapy or stem cell transplantation

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Axicabtagene ciloleucel	Single dose	1	1	1
Appropriate comparator therapy				
CAR-T cell therapy				
Tisagenlecleucel	Single dose	1	1	1
Lisocabtagene maraleucel	Single dose	1	1	1

Consumption:

For dosages depending on body weight (bw) or body surface area (BSA), 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).[3]

For the appropriate comparator therapy options tisagenlecleucel and lisocabtagene maraleucel as well as for the medicinal product to be assessed axicabtagene ciloleucel, the consumption of vials or infusion bags is presented 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 tisagenlecleucel, lisocabtagene maraleucel and axicabtagene ciloleucel are independent of the specific number of vials or infusion bags used.

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

Adults with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy, who are eligible for CAR-T cell therapy or stem cell transplantation

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					
Axicabtagene ciloleucel	< 100 kg: 1 - 2 x 10^6 viable CAR+ T cells per kg	1 - 2 x 10^6/kg CAR+ T cells	1 single infusion bag	1	1 single infusion bag
	≥ 100 kg: 2 x 10^8 Viable CAR+ T cells (from 100 kg regardless of body weight)	2 x 10^8 CAR+ T cells			
Appropriate comparator therapy					
Tisagenlecleucel	0.6 - 6 x 10^8 viable CAR+ T cells (regardless of body weight)	0.6 - 6 x 10^8 viable CAR+ T cells	1 single infusion bag	1	1 single infusion bag
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

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.

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				
Axicabtagene ciloleucel	1 single infusion bag	€ 272,000	€ 0[4]	€ 272,000.00

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					
Designation of the therapy	Packaging size	Costs (purchase price clinic pack plus value added tax)	Value added tax (19%)		Costs of the medicinal product
Tisagenlecleucel	1 single infusion bag	€ 239,000.00	€ 0[4]		€ 239,000.00
Lisocabtagene maraleucel	1 single infusion bag	€ 345,000.00	€ 0[4]		€ 345,000.00

LAUER-TAXE® last revised: 1 December 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 5a SGB V, when a non-prescription medicinal product is dispensed invoiced according Section 300, a medicinal product sale price applies to the

[4] The medicinal product is exempt from value added tax at the applied LAUER-TAXE® last revised.

insured person in the amount of the sale price of the pharmaceutical company plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the valid version of 31 December 2003.

Prophylactic premedication

Antipyretic and antihistamine premedication is only recommended in the product information of axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel.

Conditioning chemotherapy for lymphocyte depletion under CAR-T cell therapy

Axicabtagene ciloleucel, lisocabtagene maraleucel and tisagenlecleucel are autologous cell products 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 of the Medicinal Products Act (AMG), no further costs are incurred in this respect for the medicinal product to be assessed and tisagenlecleucel.

For axicabtagene ciloleucel, 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.

For tisagenlecleucel, provided the white blood cell count is not below ≤ 1,000 cells/µl one week prior to infusion, a treatment regimen for lymphocyte depletion, consisting of intravenous administration of cyclophosphamide (250 mg/m^2 = 475 mg) and fludarabine (25 mg/m^2 = 47.5 mg) is given daily for 3 days, with infusion administered 2 to 14 days after the start of lymphocyte depletion.

For lisocabtagene maraleucel, a treatment regimen for lymphocyte depletion, consisting of intravenous administration of cyclophosphamide (300 mg/m^2 = 570 mg) and fludarabine (30 mg/m^2 = 57 mg), is given daily for 3 days, with infusion administered 2 to 7 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 axicabtagene ciloleucel, lisocabtagene maraleucel or tisagenlecleucel. These investigations are equally necessary for the medicinal product to be assessed and the therapy options of the appropriate comparator therapy. Since there is no 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 corresponding costs of additionally required SHI services are not 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:							
Axicabtagene ciloleucel							
Conditioning chemotherapy for lymphocyte depletion							
Cyclophosphamide 500 mg/m² = 950 mg	6 PSI at 500 mg	€ 84.44	€ 2.00	€ 9.25	€ 73.19	3.0	€ 73.19
Fludarabine 30 mg/m² = 57 mg	1 CII at 50 mg	€ 118.54	€ 2.00	€ 5.09	€ 111.45	3.0	€ 668.70
Appropriate comparator therapy							
Tisagenlecleucel							
Conditioning chemotherapy for lymphocyte depletion							
Cyclophosphamide 250 mg/m² = 475 mg	10 PSI at 200 mg	€ 62.80	€ 2.00	€ 4.89	€ 55.91	3.0	€ 55.91
Fludarabine 25 mg/m² = 47.5 mg	1 CII at 50 mg	€ 118.54	€ 2.00	€ 5.09	€ 111.45	3.0	€ 334.35
Lisocabtagene maraleucel							
Conditioning chemotherapy for lymphocyte depletion							
Cyclophosphamide 300 mg/m² = 570 mg	10 PSI at 200 mg	€ 62.80	€ 2.00	€ 4.89	€ 55.91	3.0	€ 55.91
Fludarabine 30 mg/m² = 57 mg	1 CII at 50 mg	€ 118.54	€ 2.00	€ 5.09	€ 111.45	3.0	€ 668.70
Abbreviations: CII = concentrate for injection or infusion solution; PSI = powder for solution for injection							

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 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 SGB V.

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:

Adults with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy, who are eligible for CAR-T cell therapy or stem cell transplantation

- 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 for axicabtagene ciloleucel, Yescarta (axicabtagene ciloleucel);
Last revised: July 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 March 2023, 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 June 2023, the pharmaceutical company submitted a dossier for the benefit assessment of axicabtagene ciloleucel to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 5 VerfO.

By letter dated 3 July 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 axicabtagene ciloleucel.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 September 2023, and the written statement procedure was initiated with publication on the G-BA website on 2 October 2023. The deadline for submitting statements was 23 October 2023.

The oral hearing was held on 6 November 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 12 December 2023, and the proposed resolution was approved.

At its session on 21 December 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 March 2023	Determination of the appropriate comparator therapy
Plenum	1 June 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	1 November 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	6 November 2023	Conduct of the oral hearing
Working group Section 35a	15 November 2023 6 December 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	12 December 2023	Concluding discussion of the draft resolution
Plenum	21 December 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 21 December 2023

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

Prof. Hecken