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 after the deadline: diffuse large B-cell lymphoma, high-grade B-cell lymphoma, after 1 prior therapy, relapsed within 12 months or refractory)

of 19 December 2024

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 all 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 pharmaceutical company submitted a dossier on 1 July 2023 for the early benefit assessment of the active ingredient axicabtagene ciloleucel (Yescarta) on 1 July 2023. For the resolution of 21 December 2023 passed by the G-BA in this procedure, a limitation was announced for patient population a (patients eligible for high-dose therapy) until 1 July 2024.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Yescarta recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO on 27 June 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 October 2024 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 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 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:

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 diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

Therapeutic indication of the resolution (resolution of 19 December 2024):

Yescarta is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are eligible for high-dose therapy and who relapse within 12 months from completion of, or are refractory to, first-line therapy.

2.1.2 Appropriate comparator therapy

a) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are 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 axicabtagene ciloleucel:

Induction therapy with

- R-GDP (rituximab, gemcitabine, cisplatin, dexamethasone) *or*

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

- 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]

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 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.

[2] Taking into account the requirements of the Directive on Inpatient Treatment Methods (last revised 20 November 2024): Section 4, paragraph 2, number 4

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 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 vindesine have the marketing authorisation for the superordinate 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 lisocabtagene maraleucel 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.

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. In the present therapeutic indication, the following resolutions or guidelines of the G-BA are available:

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

- Lisocabtagene maraleucel (resolution of 16 November 2023)
- Tafasitamab (resolution of 3 March 2022)
- Polatuzumab vedotin (resolution of 20 August 2020)
- Pixantrone (resolution of 16 May 2013)

Directive on 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-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. 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 present benefit assessment procedure (reassessment after the deadline) relates exclusively to the group of patients eligible for high-dose therapy (patient group a) of the resolution on the benefit assessment of the active ingredient axicabtagene ciloleucel of 21 December 2023):

a) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are eligible for high-dose therapy and who relapse 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 later approved for the second-line treatment of B-cell lymphomas in close proximity to each other and subject to benefit assessment. In the benefit assessment, a hint for a considerable additional benefit of lisocabtagene maraleucel compared with induction chemotherapy with R-GDP, R-ICE or R-DHAP followed by high-dose therapy with autologous stem cell transplantation was identified (resolution of 16 November 2023). 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 axicabtagene ciloleucel 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, and HGBL following first-line therapy. In addition, allogeneic stem cell transplantation can be considered as consolidation in accordance with the Directive on Inpatient Treatment Methods[3], 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 recommendations of the S3 guidelines, these treatment regimes were compared with each other in prospective randomised studies, whereby differences in toxicity were found with the same efficacy.[4,5] 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.[6] 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[7]. 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.

---

3 Last revised 18 October 2023

4 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

5 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.

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

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

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). The determination of CAR-T cell therapy in accordance with the guideline recommendations is not an option for the present resolution, taking into account Section 6, paragraph 2, sentence 2 SGB V. 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 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.

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.

2.1.3 Extent and probability of the additional benefit

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

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

Hint for a minor additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company submits results of the ZUMA-7 study. In the ongoing, open-label phase III ZUMA-7 study, axicabtagene ciloleucel is being compared with induction therapy with R-ICE, R-DHAP, R-ESHAP and R-GDP followed by high-dose chemotherapy (HDCT) with autologous stem cell transplantation (SCT). The study has been conducted in 77 study sites in Australia, Asia, Europe and North America since January 2018.

Adults with DLBCL and HGBL with refractory or relapsed disease within 12 months of completing first-line therapy consisting of rituximab and anthracycline-based chemoimmunotherapy were enrolled in the study. In addition, the aim had to be to continue with HDCT and autologous SCT if the patients responded to induction therapy, were in good

general condition (ECOG-PS 0-1), had adequate organ function and radiologically documented disease.

A total of 359 patients were enrolled - stratified by response to first-line therapy (primary refractory vs relapse ≤ 6 months vs relapse > 6 and ≤ 12 months after first-line therapy) and by secondary age-adjusted international prognostic index (sAAIPI) (0 or 1 vs 2 or 3) - randomised in a 1:1 ratio to either treatment with axicabtagene ciloleucel (N = 180) or induction + HDCT + autologous SCT (N = 179).

The treatment with axicabtagene ciloleucel was carried out according to the requirements in the product information. In the period between leukapheresis and lymphodepletion, patients could receive bridge therapy with corticosteroids as required by the principal investigator. Bridge therapy in the form of chemoimmunotherapy was not permitted in the ZUMA-7 study. Patients with disease progression after a previous response on day 50 could again be administered lymphodepletion and treated with axicabtagene ciloleucel.

In the comparator arm, patients initially received induction therapy with 2 to 3 cycles of R-ICE, R-DHAP, R-ESHAP or R-GDP at the principal investigator's discretion. Patients who achieved a partial or complete response to therapy according to the Lugano classification (Cheson et al.; 2014) after 2 to 3 cycles of induction therapy (around day 50) subsequently received HDCT and autologous SCT.

Subsequent antineoplastic therapies were at the discretion of the principal investigator in both study arms and were possible without limitation. Overall, 49% of patients in the intervention arm and 72% in the comparator arm received at least 1 subsequent therapy at the 2nd data cut-off, including chemo(immuno)therapy (81%) and high-dose therapy followed by autologous SCT (15%) in the intervention arm and autologous CD19-CAR-T therapy (77%) in the comparator arm.

The primary endpoint of the ZUMA-7 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.

Two data cut-offs have been carried out so far. The data cut-off from 18.03.2021 is the primary EFS analysis and 1st interim analysis for overall survival. The data cut-off from 25.01.2023 was the final analysis of overall survival.

On the implementation of conditions for a time limit

According to the justification for the resolution of 21 December 2023, the reason for the time limit was that the evaluations on adverse events from the pivotal ZUMA-7 study submitted by the pharmaceutical company were unsuitable for the benefit assessment due to an inappropriate analysis population for the presented results on side effects, which is why it was not possible to carry out a benefit-risk assessment of axicabtagene ciloleucel on the basis of the data presented.

For the benefit reassessment after the deadline, evaluations of all endpoints (incl. time-to-event analyses) on adverse events in the ZUMA-7 study must be presented based on an analysis population that not only includes patients in the intervention arm who received an infusion with axicabtagene ciloleucel, but also includes adverse events during the preparatory processes, i.e. leukapheresis, bridge therapy and lymphodepletion.

Furthermore, the results on all patient-relevant endpoints from the ZUMA-7 study that are used to demonstrate an additional benefit must be presented in the dossier for the benefit reassessment after the deadline.

The pharmaceutical company presented the required evaluations in the dossier, so that the time limit requirements are considered to have been implemented overall.

Implementation of the appropriate comparator therapy

In the comparator arm of the ZUMA-7 study, R-DHAP, R-ICE, R-ESHAP or R-GDP was used with subsequent HDCT and SCT. The R-ESHAP regimen administered in the ZUMA-7 study is not explicitly mentioned in the S3 guideline, but was only used in 3% of patients in the study. Overall, the appropriate comparator therapy is assessed as implemented.

On the implementation of the ZUMA-7 study

In the European Public Assessment Report (EPAR) for axicabtagene ciloleucel in the present therapeutic indication, the European Medicines Agency (EMA) points out that it was not ensured during the course of the study that the conduct and monitoring of the study were shielded from each other, although the integrity of the ZUMA-7 study is not called into question by the EMA[8]. IQWiG identified a high risk of bias across endpoints in this regard. Thus, it is not certain whether the protocol changes in Amendment 5, which reduced the triggers for the primary EFS analysis from 270 to 250 EFS events and for the first OS analysis from 140 to 110 deaths, were made without knowledge of the data. The pharmaceutical company explains that the protocol changes in Amendment 5 were triggered based on the available pooled and blinded data and justified by a plateau in observed EFS events across both study arms. This explanation seems plausible. It was found that only very few EFS events additionally occurred between the primary EFS analysis (1st data cut-off) and the 2nd data cut-off. Although the uncertainty described by IQWiG is included in the present assessment, no high risk of bias is derived for all study endpoints based on this alone.

In addition, only the administration of corticosteroids as a bridge therapy between leukapheresis and axicabtagene ciloleucel infusion was permitted in the ZUMA-7 study. This approach in the ZUMA-7 study is considered acceptable for the benefit assessment against the background of the explanations by the clinical assessment experts. The clinical experts explained in their statements that the question of bridge therapy, in particular in the second-line therapy, is not completely clarified. The recommendation of the S3 guideline in favour of bridge therapy with platinum-containing chemoimmunotherapy is based on consensus and not on evidence, and relates exclusively to third-line therapy. Even the evidence now available for second-line treatment from the ZUMA-7, TRANSFORM and BELINDA studies cannot conclusively demonstrate any advantages of a specific bridge therapy. There is no increased uncertainty for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

The overall survival was operationalised in the ZUMA-7 study as the time from randomisation to death from any cause.

The endpoint of overall survival is used for the present benefit assessment. There was a statistically significant difference to the advantage of axicabtagene ciloleucel in this case. The extent of the prolongation of survival time is assessed as a minor improvement.

[8] European Medicines Agency. Yescarta; Assessment report [online]. 2022 [accessed: 19.11.2024]. https://www.ema.europa.eu/documents/variation-report/yescarta-h-c-004480-ii-0046-epar-assessment-report-variation_en.pdf.

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 could be 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 therapeutic approach.

In the dossier for the benefit assessment, the pharmaceutical company presented two new modified operationalisations (mEFS1 and mEFS2) of this endpoint in addition to the EFS (primary endpoint of the study). There are uncertainties in the original analyses on the EFS endpoint regarding the non-performance of a stem cell transplant after induction therapy in patients with CR or PR in the comparator arm. In this context, uncertainties exist also with regard to the component "Initiation of new lymphoma therapy" as to whether some of the patients in the comparator arm had reasons that did not necessarily represent a failure of the curative therapeutic approach.

In the two post-hoc defined modified EFS (mEFS1 and mEFS2), these relevant uncertainties of the EFS endpoint are adequately addressed by the pharmaceutical company.

The mEFS1 is defined as the time between the day of randomisation and the time of occurrence of the first of the following events:

- Death from any cause
- Progression of the disease (after blinded centralised assessment)
- Failure to achieve complete remission (CR) or partial remission (PR) until day 50 in the comparator arm (after blinded centralised assessment)
- Failure to achieve a CR on day 150 according to blinded centralised assessment (or, if applicable, up to and including month 9)
- Initiation of new lymphoma therapy due to stable disease (SD) or PD according to the principal investigator

The mEFS 2 is defined as the time between the day of randomisation and the time of occurrence of the first of the following events:

- Death from any cause
- Progression of the disease (after blinded centralised assessment)
- Failure to achieve a CR or PR until day 50 in the comparator arm (after blinded centralised assessment)
- Failure to achieve a CR on day 150 according to blinded centralised assessment (or, if applicable, up to and including month 9)
- Initiation of new lymphoma therapy with previous SD after blinded centralised assessment

The two operationalisations differ only in the component "Initiation of new lymphoma therapy" (SD or PD according to principal investigator vs previous SD according to blinded centralised assessment).

Based on the existing operationalisations of the mEFS1 and mEFS2, the percentage of patients with an event and thus the relative risk (RR) is considered the relevant effect size. The presented time-to-event analyses (hazard ratio, HR) are inherently biased by the endpoint

operationalisations, since the component "Failure to achieve a CR or PR until day 50" is only included in the analysis in the comparator arm and failure can therefore be attained significantly earlier than in the intervention arm, so that the HR cannot be interpreted in the present case.

In addition, it should be noted that there are uncertainties regarding a discrepancy in the comparator arm for the EFS endpoint with regard to the respective qualifying events between the assessment according to the principal investigator and blinded centralised assessment. In this regard, the objective response assessments for 28 (19%) of the patients on day 50 differed between the principal investigator and centralised assessment (19 patients without response according to the principal investigator's assessment, but with response according to blinded centralised assessment; 9 patients with response according to the principal investigator's assessment, but without response according to blinded centralised assessment).

Thus, mEFS1 events in which the achievement of SD or PD is based on the principal investigator's assessment are subject to uncertainty. In contrast, a centralised assessment is not available for all patients on day 50 although only events based on blinded centralised assessment are included in the mEFS2.

As part of the written statement procedure, the pharmaceutical company submitted revised analyses of mEFS1 and mEFS2, referred to as mEFS1.1/1.2 and mEFS2.1/2.2.

In the mEFS1.1 and mEFS2.1 analyses, the component "Failure to achieve a complete response [CR] until day 150 according to the blinded centralised assessment (or, if applicable, by month 9)" was extended to month 18. In particular, this shows that 4 patients still achieved a CR after month 9 without subsequent therapy and are therefore no longer included as events in the analysis. In addition, a patient who had progression according to blinded centralised assessment but later achieved a CR without starting a new therapy is also no longer included as an event in the analyses.

In the analyses of mEFS1.2 and mEFS2.2, the pharmaceutical company removed the component "Failure to achieve a CR or partial response (PR) according to the blinded centralised assessment until day 50 in the comparator arm".

In the overall assessment, compared to the mEFS1 and mEFS2 analyses presented in the dossier, these subsequently submitted analyses do not offer any significant gain in knowledge and are also incomplete due to the lack of subgroup analyses and Kaplan-Meier curves. In addition, the time-to-event analyses remain inherently biased, so that the HR is still not interpretable.

As a result, despite existing uncertainties, the joint consideration of the mEFS1 and mEFS2 analyses is considered sufficiently suitable to derive conclusions regarding the failure of the curative therapeutic approach, which is why these analyses are used as the basis for the assessment. On this basis, an advantage of axicabtagene ciloleucel over induction + HDCT + autologous SCT is identified, the extent of which is considered to be a minor improvement.

Symptomatology (EORTC QLQ-C30) and health status (EQ-5D VAS)

In the dossier, the pharmaceutical company submits evaluations of symptomatology assessed using the symptom scales of the EORTC-QLQ-C30 questionnaire and the health status assessed using the EQ-5D VAS at the 1st data cut-off from 18.03.2021. In the dossier, no data on the relevant 2nd data cut-off were submitted.

Overall, there are uncertainties regarding the data quality and evaluability of the patient-reported endpoints collected in the ZUMA-7 study:

The percentage of missing values increases sharply over the course of the study, so that by the time of the survey on day 100, only < 50% of the randomised patients in the comparator arm are included in the evaluations. In addition, there is a high differential percentage of patients missing from the evaluation.

For these reasons, the results on the endpoints on symptomatology and health status are not used for the benefit assessment.

Quality of life

Quality of life was assessed in the ZUMA-7 study using the functional scales of the EORTC-QLQ-C30 questionnaire.

Reference is made to the above statements on the symptomatology endpoint. The results on health-related quality of life are not used for the benefit assessment.

Side effects

In the ZUMA-7 study, adverse events (AEs) were collected until study day 150 or until switching to another lymphoma therapy, whichever occurred first.

The dossier presented analyses of all endpoints on AEs (including time-to-event analyses) for a modified safety analysis set, which included all patients from the time of leukapheresis in the intervention arm and all patients who received at least one dose of induction chemotherapy in the comparator arm.

Adverse events in total
In the ZUMA-7 study, AEs occurred in both treatment arms in all patients. The results were only presented additionally.

Serious AEs (SAEs) and severe AEs
For the overall rate of SAEs and severe AEs, there was no statistically significant difference between the study arms.

Discontinuation due to AEs
No information on effect estimator is available for the endpoint of discontinuation due to AEs. However, only very few events occurred in both study arms, so that a statistically significant difference between the study arms can be ruled out.

Specific AEs
With regard to specific AEs, there was a statistically significant advantage of axicabtagene ciloleucel for the endpoints of febrile neutropenia (SAE), thrombocytopenia and gastrointestinal disorders (severe AE in each case), ear and labyrinth disorders, mucositis and hiccup.

There was a statistically significant disadvantage of axicabtagene ciloleucel for the specific AEs of general disorders and administration site conditions, neutropenia, psychiatric disorder and hypotension (severe AE in each case), severe neurological toxicity, cough and hypoxia.

For the endpoint of severe infections, there was no statistically significant difference between the treatment arms.

For the specific AE of thrombocytopenia (severe AE), there was an effect modification for the age characteristic. For patients < 65 years of age, there was a statistically significant difference in favour of axicabtagene ciloleucel. For patients ≥ 65 years of age, there was no statistically significant difference between the study arms. In addition, there was an effect modification

for the sAAIPI characteristic for the specific AE of cough. For patients with sAAIPI 0-1, there was no statistically significant difference between the study arms, while for patients with sAAIPI 2-3, there was a statistically significant difference to the disadvantage of axicabtagene ciloleucel.

In the overall analysis of the results, neither an advantage nor a disadvantage of treatment with axicabtagene ciloleucel compared to induction chemotherapy with R-GDP, R-ICE or R-DHAP followed by high-dose therapy with autologous stem cell transplantation was found overall with regard to the results for side effects.

Overall assessment

For the benefit assessment of axicabtagene ciloleucel, data are available from the open-label, randomised phase III ZUMA-7 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.

For the overall survival, there is a statistically significant difference in favour of axicabtagene ciloleucel. The extent of the prolongation of survival time is assessed as a minor improvement.

Since the 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 is used to illustrate the failure of the curative therapeutic approach. In this respect, the assessment is based on the post-hoc defined analyses of the EFS (mEFS1 and mEFS2). Based on these results, an advantage of axicabtagene ciloleucel is identified, the extent of which is assessed as a minor improvement.

No suitable data is available on symptomatology (assessed using the EORTC-QLQ-C30) and health status (assessed using the EQ-5D-VAS) due to an excessively high percentage of missing values and the high differential percentage of patients missing from the evaluation. 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 were both advantages and disadvantages of axicabtagene ciloleucel for the specific AEs.

In the overall assessment, a minor additional benefit of axicabtagene ciloleucel compared with induction chemotherapy with R-GDP, R-ICE or R-DHAP followed by high-dose therapy with autologous stem cell transplantation was therefore identified for the treatment of DLBCL and HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy, in patients who are eligible for high-dose therapy.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the ongoing open-label, randomised, phase III ZUMA-7 study. The risk of bias at the study level is rated as low.

There is uncertainty regarding the component "Initiation of new lymphoma therapy" for the EFS endpoint, which may have a bias effect on overall survival.

For the mEFS endpoint, there are uncertainties regarding a discrepancy in the comparator arm with regard to the respective qualifying events between the principal investigator's assessment and the blinded centralised assessment.

Further limitations result from the fact that no suitable data are available for the patient-reported endpoints on symptomatology, assessed with the EORTC QLQ-C30, and health status, assessed with the EQ-5D VAS, as well as on 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.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient axicabtagene ciloleucel due to the expiry of the limitation of the resolution of 21 December 2023. The assessment exclusively refers to the use of axicabtagene ciloleucel for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy in the following patient population:

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

Data from the phase III ZUMA-7 study for comparing axicabtagene ciloleucel with induction therapy (R-ICE, R-DHAP, R-ESHAP or R-GDP) + HDT + autologous SCT are available for this patient group.

For the overall survival, there is a statistically significant difference in favour of axicabtagene ciloleucel. The extent of the prolongation of survival time is assessed as a minor improvement.

Since the patients in the present therapeutic indication are treated with a curative therapeutic approach, the failure of a curative therapeutic approach is fundamentally patient-relevant. Based on the results of the post-hoc modified evaluations for the endpoint of event-free survival (mEFS1 and mEFS2), an advantage of axicabtagene ciloleucel was found with regard to the failure of the curative therapeutic approach, the extent of which was assessed as a minor improvement.

No suitable data are available on symptomatology (assessed using the EORTC-QLQ-C30) and health status (assessed using the EQ-5D-VAS). 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 were both advantages and disadvantages of axicabtagene ciloleucel for the specific AEs.

In the overall assessment, a minor additional benefit was identified for axicabtagene ciloleucel compared with induction chemotherapy with R-GDP, R-ICE or R-DHAP followed by high-dose therapy with autologous stem cell transplantation.

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

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 patient numbers presented by the pharmaceutical company in the dossier is subject to uncertainties.

In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a

basis in the resolution on the benefit assessment of lisocabtagene maraleucel (resolution of 16 November 2023)[9]. A more valid estimate of the number of patients in the SHI target population is available here; this can be used despite continuing uncertainties.

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 December 2024):

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 pass. 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).

A Direct Healthcare Professional Communication ("Rote-Hand-Brief") which reports on the occurrence of secondary malignancies of T-cell origin, including chimeric antigen receptor (CAR)-positive malignancies, is available for the currently approved CD19- or BCMA-targeted CAR T-cell therapies. Patients who have been treated with CAR-T cell products should therefore be monitored throughout their lives for the occurrence of secondary malignancies.

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 2024).

For the cost representation, 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 co-morbidities) are not taken into account when calculating the annual treatment costs.

[9] Benefit assessment procedure D-951 of lisocabtagene maraleucel

CAR-T cell therapies

Axicabtagene ciloleucel 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 for these active ingredients as treatment options of the medicinal product to be assessed.

Axicabtagene ciloleucel is listed on LAUER-TAXE®, but is only dispensed to appropriate qualified inpatient treatment facilities, and administered there. 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.

Axicabtagene ciloleucel 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[10]. Furthermore, for the treatment regimens and dosages in relation to the combination therapy R-GDP, the study by Crump et al. (2014)[5] 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)[11] are taken into account.

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 2024 (€ 4210.59). 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 for 2024 according to Section 15 para. 2a KHEntgG (Act on Fees for Full and Semi-inpatient Hospital Services) (€ 250) and the treatment-specific nursing fee valuation ratio.

Treatment period:

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

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

[11] 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				
Axicabtagene ciloleucel	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)[5]				
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)[11]				
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)[5, 11]				
Rituximab	1 x per 21-day cycle (day 1; additionally	2 - 3	1	2 – 4

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	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)[5]				
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)[11]				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
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)[5, 11]				
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

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916).[12]

The consumption of vials and infusion bags is presented for the medicinal product to be assessed, axicabtagene ciloleucel, 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 axicabtagene ciloleucel are independent of the specific number of vials or infusion bags used.

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/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					
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)[5]					
Rituximab	375 mg/m² = 716.3 mg	716.3 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 = 1,910 mg	1,910 mg	1 x 2,000 mg	4 – 6	4.0 x 2,000 mg – 6.0 x 2,000 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	8 – 12	8.0 x 40 mg – 12.0 x 40 mg

[12] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), 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
Cisplatin	75 mg/m² = 143.3 mg	143.3 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)[11]					
Rituximab	375 mg/m² = 716.3 mg	716.3 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 = 9,550 mg	9,550 mg	2 x 5,000 mg	2 – 3	4.0 x 5,000 mg – 6.0 x 5,000 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 = 191 mg	191 mg	1 x 200 mg	6 – 9	6.0 x 200 mg – 9.0 x 200 mg
R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin)[5, 11]					
Rituximab	375 mg/m² = 716.3 mg	716.3 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
Dexamethasone	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 3,820 mg	7,640 mg	4 x 2,000 mg	2 – 3	8.0 x 2,000 mg – 12.0 x 2,000 mg
Cisplatin	100 mg/m² = 191 mg	191 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)[5]					
Rituximab	375 mg/m² = 716.3 mg	716.3 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 = 1,910 mg	1,910 mg	1 x 2,000 mg	4 – 6	4.0 x 2,000 mg – 6.0 x 2,000 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	8 – 12	8.0 x 40 mg – 12.0 x 40 mg
Cisplatin	75 mg/m² = 143.3 mg	143.3 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)[11]***Fehler! Textmarke nicht definiert.***					
Rituximab	375 mg/m² = 716.3 mg	716.3 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 = 9,550 mg	9,550 mg	2 x 5,000 mg	2 – 3	4.0 x 5,000 mg – 6.0 x 5,000 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 = 191 mg	191 mg	1 x 200 mg	6 – 9	6.0 x 200 mg – 9.0 x 200 mg
R-DHAP (rituximab + dexamethasone + cytarabine + cisplatin)[5, 11]					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Rituximab	375 mg/m² = 716.3 mg	716.3 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
Dexamethasone	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 3,820 mg	7,640 mg	4 x 2,000 mg	2 – 3	8.0 x 2,000 mg – 12.0 x 2,000 mg
Cisplatin	100 mg/m² = 191 mg	191 mg	2 x 100 mg	2 – 3	4.0 x 100 mg – 6.0 x 100 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 reference prices 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									
2024	R61G	7.6	1.005	€ 4,210.59	0.7749	€ 250	€ 4,228.18	€ 1,472.31	€ 4,231.64
2024	A04E	34.4	8.985	€ 4,210.59	1.9317	€ 250	€ 37,801.15	€ 16,612.62	€ 37,832.15
High-dose chemotherapy with autologous stem cell transplantation									
2024	A42A	16.1	1.986	€ 4,210.59	0.7507	€ 250	€ 8,355.38	€ 3,021.57	€ 8,362.23
2024	A15C	23.8	5.303	€ 4,210.59	1.2410	€ 250	€ 22,310.46	€ 7,383.95	€ 22,328.76

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[13]	€ 272,000

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	1 CIS	€ 1,777.34	€ 2.00	€ 84.18	€ 1,691.16
Rituximab 100 mg	2 CIS	€ 717.21	€ 2.00	€ 33.50	€ 681.71
Gemcitabine					
Gemcitabine 2000 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					
Cisplatin 100 mg	1 CIS	€ 76.59	€ 2.00	€ 3.10	€ 71.49
Cisplatin 50 mg	1 CIS	€ 47.71	€ 2.00	€ 1.73	€ 43.98
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 SFI	€ 77.06	€ 2.00	€ 3.12	€ 71.94
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection/infusion; TAB = tablets					

LAUER-TAXE® last revised: 1 December 2024

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

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 axicabtagene ciloleucel.

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

Conditioning chemotherapy for lymphocyte depletion under CAR-T cell therapy

Axicabtagene ciloleucel 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, no further costs are incurred in this respect for axicabtagene ciloleucel.

For axicabtagene ciloleucel, a treatment regimen for lymphocyte depletion, consisting of intravenous administration of cyclophosphamide (500 mg/m^2 = 955 mg) and fludarabine (30 mg/m^2 = 57.3 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 axicabtagene ciloleucel. 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.

Diagnostics to rule out chronic hepatitis B requires sensibly coordinated steps. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. In certain case constellations, further steps may be necessary in accordance with current guideline

recommendations[14].

Diagnostics to rule out hepatitis C requires sensibly coordinated steps. HCV screening is based on the determination of anti-HCV antibodies. In certain case constellations, it may be necessary to verify the positive anti-HCV antibody findings in parallel or subsequently by HCV-RNA detection to confirm the diagnosis of an HCV infection[15].

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 = 955 mg	6 PSI at 500 mg	€ 84.44	€ 2.00	€ 9.25	€ 73.19	3.0	€ 73.19
Fludarabine 30 mg/m² = 57.3 mg	1 CII at 50 mg	€ 118.54	€ 2.00	€ 5.09	€ 111.45	3.0	€ 668.70
Screening for HBV, HCV and HIV							
HBV test Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Hepatitis C HCV antibody status (GOP 32618)	-	-	-	-	€ 9.80	1.0	€ 9.80
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							
HBV test	-	-	-	-	€ 5.50	1.0	€ 5.50

[14] S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011 https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf].

[15] S3 guideline on prevention, diagnosis and therapy of hepatitis C virus (HCV) infection; AWMF registry no.: 021/012 https://register.awmf.org/assets/guidelines/021-012l_S3_Hepatitis-C-Virus_HCV-Infektion_2018-07.pdf].

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
Hepatitis B Surface antigen status (GOP number 32781)							
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	€ 5.02	€ 16.70	2.0 – 3.0	€ 16.70 – € 33.40
Paracetamol[16] (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-DHAP)							
Dimetindene (1 mg/10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.02	€ 16.70	2.0 – 4.0	€ 16.70 – € 33.40
Paracetamol[16] (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
Premedication (R-ICE)							
Dimetindene (1 mg/10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.02	€ 16.70	2.0 – 4.0	€ 33.40
Paracetamol[16] (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
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 250 ml INF	€ 87.05	€ 4.35	€ 7.94	€ 74.76	2.0 – 3.0	€ 74.76

[16] 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
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 – € 41.84
	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05		
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						
	5 SFI x 1,000 mg	€ 66.24	€ 2.00	€ 6.95	€ 57.29	2.0 – 3.0	€ 114.58 – € 171.87
	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 x 400 mg	€ 148.19	€ 2.00	€ 17.33	€ 128.86	2.0 – 3.0	€ 300.73 - € 372.30
	5 SFI x 1,000 mg	€ 66.24	€ 2.00	€ 6.95	€ 57.29		
Abbreviations: AMP = ampoules; SFI = solution for injection; INF = infusion solution							

LAUER-TAXE® last revised: 01 December 2024

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 agents 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 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 requirements 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:

a) Adults with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) who are eligible for high-dose therapy and who relapse 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 for axicabtagene ciloleucel (Yescarta); product information for Yescarta; last revised: November 2024

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

The plenum determined the appropriate comparator therapy at its session on 21 December 2023.

On 27 June 2024, 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 28 June 2024 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 24 September 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 October 2024. The deadline for submitting statements was 22 October 2024.

The oral hearing was held on 11 November 2024.

By letter dated 12 November 2024, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 27 November 2024.

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 10 December 2024, and the proposed draft resolution was approved.

At its session on 19 December 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Plenum	21 December 2023	Determination of the appropriate comparator therapy
Working group Section 35a	5 November 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 November 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	19 November 2024 3 December 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	10 December 2024	Concluding discussion of the draft resolution
Plenum	19 December 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 December 2024

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

Prof. Hecken