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 (new therapeutic indication: follicular lymphoma, after ≥ 3 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

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.

On 21 June 2022, axicabtagen-ciloleucel received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing

authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

Yescarta for the treatment of relapsed or refractory (r/r) follicular lymphoma (FL) after three or more lines of systemic therapy is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) number 141/2000 of the European Parliament and of the Council of 16 December 1999.

On 14 November 2022, the pharmaceutical company submitted the dossier to the G-BA for benefit assessment in accordance with Section 35a, paragraph 1, sentence 11 SGB V on time.

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 for a limited period of time. 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 due time on 30 June 2023 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 the active ingredient axicabtagene ciloleucel with the new therapeutic indication*:* "Yescarta is indicated for the treatment of adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) after three or more lines of systemic therapy".

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 7.0 from 19.09.2023. 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) follicular lymphoma (FL) after three or more lines of systemic therapy.

Therapeutic indication of the resolution (resolution of 21 December 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) follicular lymphoma after three or more lines of systemic therapy

Appropriate comparator therapy:

Patient-individual therapy with selection of:

- Bendamustine + obinutuzumab followed by obinutuzumab maintenance treatment in accordance with the marketing authorisation,
- Lenalidomide + rituximab,
- Rituximab monotherapy,
- Mosunetuzumab,
- Tisagenlecleucel

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

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.

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

on 1. In terms of authorisation status, the following active ingredients are available for the treatment of (grades 1 to 3a) follicular lymphoma:

Medicinal products with explicit marketing authorisation for the treatment of (relapsed or refractory) follicular lymphoma: Duvelisib, ibritumomab tiuxetan, interferon alfa-2a, interferon alfa-2b, lenalidomide, obinutuzumab, rituximab, mosunetuzumab, tisagenlecleucel and axicabtagene ciloleucel. With regard to the active ingredients interferon alfa-2a, duvelisib and ibritumomab tiuxetan, it should be noted that these are currently off the market in Germany.

Follicular lymphoma is to be assigned to indolent non-Hodgkin lymphoma. The cytostatic agents bendamustine, bleomycin, chlorambucil, cyclophosphamide, cytarabine, doxorubicin, etoposide, methotrexate, mitoxantrone, trofosfamide, vinblastine and vincristine; as well as the glucocorticoids dexamethasone, methylprednisolone, prednisolone and prednisone have a marketing authorisation for the treatment of indolent non-Hodgkin lymphoma.

Medicinal products with explicit marketing authorisation for the treatment of high-grade non-Hodgkin lymphoma and grade 3b follicular lymphoma were not included.

on 2. Non-medicinal treatments for follicular lymphoma include radiotherapy, autologous stem cell transplantation and allogeneic stem cell transplantation.

on 3. In the therapeutic indication of follicular lymphoma, the following resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- Obinutuzumab (resolution of 4 November 2021)
- Idelalisib (resolution of 19 March 2015)
- Duvelisib (resolution of 21 July 2022)
- Tisagenlecleucel (resolution of 1 December 2022)
- Mosunetuzumab (resolution of 15 December 2022)

Furthermore, there is a resolution on Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (so-called off-label use):

- Use of fludarabine in low or intermediate-grade B-non-Hodgkin lymphoma (B-NHL) other than chronic lymphocytic leukaemia (CLL) as specified in the marketing authorisation

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 indication according to Section 35a paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy").

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 appropriate comparator therapy determined on the basis of this information is explained further below.

Firstly, it should be noted that, irrespective of the fact that grade 3b follicular lymphoma is formally covered by the approved therapeutic indication, the present determination of the appropriate comparator therapy relates to relapsed or refractory grade 1 to 3a follicular lymphoma. This is due to the fact that grade 3b follicular lymphoma is not classified as indolent non-Hodgkin lymphoma according to the generally recognised state of medical knowledge and is treated in the same way as diffuse large B-cell lymphoma (DLBCL). In addition, patients with grade 3b follicular lymphoma were not investigated in the ZUMA-5 study. Axicabtagene ciloleucel has a separate marketing authorisation for the treatment of patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. This approach is also supported by the new WHO classification 2022[2]

2 Allaggio R., Amador C.; Anagnostopoulos I.; The 5th edition of the World Health Organization Classification of Haematolyphoid Tumours: Lymphoid Neoplasms; Leukemia (2022)

of lymphoid tumours, which uses the new term "follicular large cell lymphoma" to distinguish the entity formerly known as "grade 3b follicular lymphoma" from the classic (grades 1 to 3a) follicular lymphoma.

Moreover, in the present therapeutic indication, it is assumed that the patients with follicular lymphoma have an indication for systemic antineoplastic therapy due to a correspondingly extensive-stage of the disease, in particular with regard to a symptomatic course (e.g. according to the GELF criteria), and therefore, among other things, a watch-and-wait strategy is not considered.

It is also assumed that there is no indication for radiotherapy at the time of treatment.

Both the current guidelines and the written statements of the scientific-medical societies indicate that there is no standard therapy in this therapeutic indication. Instead, a patient-individual therapy, which is based on various factors (including previous therapy, time to recurrence and comorbidities), is used. In the current guidelines, various therapy options for the treatment of relapsed or refractory follicular lymphoma are mentioned.[3]

The statements of the scientific-medical societies in the present procedure indicate that chemoimmunotherapies containing rituximab generally play a subordinate role particularly for patients who have already relapsed several times according to the present therapeutic indication as they have already been used in previous lines of treatment for relapse. The current guidelines for therapy in this therapeutic indication also indicate that obinutuzumab-containing induction and maintenance treatments should be used in patients with rituximab-refractory follicular lymphoma, so that it is assumed that corresponding obinutuzumab-containing therapies may also be a suitable therapy option in later relapses. With regard to chemoimmunotherapies, obinutuzumab, which is approved in combination with bendamustine as induction therapy with subsequent obinutuzumab maintenance treatment, is therefore designated as a therapy option for patient-individual therapy.

If chemoimmunotherapy is not indicated, particularly in older or co-morbid patients, monotherapy with rituximab can also be carried out in the relapsed treatment setting.

The current guidelines also refer to other therapy options: The combination of lenalidomide and rituximab may be considered if patients are refractory after chemoimmunotherapy or only in remission for a short time.

In the current guidelines, the option of high-dose therapy followed by allogeneic stem cell transplantation is still mentioned for the relapsed/refractory treatment setting. However, taking into account the present therapeutic indication after three or more previous therapies, it can be assumed that allogeneic stem cell transplantation is generally not an option and is only indicated in individual cases. This was also evident from the statements submitted by the scientific-medical societies in the present benefit assessment procedure.

3 Oncology guideline programme, German Cancer Society (DKG), German Cancer Aid (DKH), Association of the Scientific-Medical Societies in Germany (AWMF). S3 guideline - Diagnostics, therapy and after-care for patients with follicular lymphoma 2020.

According to the statements of scientific-medical societies in the present procedure, treatments with CAR-T cells and bi-specific antibodies are relevant treatment options in the present therapeutic indication (follicular lymphoma, after ≥ 3 lines of therapy).

In addition to axicabtagene ciloleucel, the CAR-T cell therapy with tisagenlecleucel and the bi-specific antibody mosunetuzumab are approved in this therapeutic indication.

For tisagenlecleucel (resolution of 1 December 2022) and mosunetuzumab (resolution of 15 December 2022), a hint for a non-quantifiable additional benefit was identified within the scope of orphan drug assessments because the scientific data did not allow quantification. The period of validity of the resolution on tisagenlecleucel is limited to 1 September 2028.

Tisagenlecleucel and mosunezutumab are determined as treatment options for patient-individual therapy, taking into account the recommendations from current guidelines and the statements of the scientific-medical societies on the significance of CAR-T cells and bi-specific antibodies in treatment.

Overall, for the present treatment setting for the named therapeutic indication, the G-BA determines a patient-individual therapy as an appropriate comparator therapy, with the selection of:

- Bendamustine + obinutuzumab followed by obinutuzumab maintenance treatment in accordance with the marketing authorisation,
- Lenalidomide + rituximab,
- Rituximab monotherapy,
- Tisagenlecleucel,
- Mosunetuzumab

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

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:

Adults with relapsed or refractory (r/r) follicular lymphoma after three or more lines of systemic therapy

Appropriate comparator therapy for axicabtagene ciloleucel

Patient-individual therapy with selection of:

- Bendamustine,
- CHOP,
- CVP,
- Chlorambucil,
- Cyclophosphamide,
- MCP,
- FCM + rituximab

followed by rituximab maintenance treatment if there is a response to induction therapy;

- Bendamustine + obinutuzumab followed by obinutuzumab maintenance treatment in accordance with the marketing authorisation,
- Lenalidomide + rituximab,
- Rituximab monotherapy
- [90Y]-radio-labelled ibritumomab tiuxetan

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

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 follicular lymphoma after three 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 was considered as an appropriate comparator therapy, a review of the appropriate comparator therapy under the regulations after the entry into force of the ALBVVG was necessary. This concerned some of the named chemo and chemo-immunotherapies.

In this regard, the statements of the scientific-medical societies in the present benefit assessment procedure however indicate that rituximab-containing chemoimmunotherapies generally play a subordinate role particularly for patients who have already relapsed several times according to the present therapeutic indication as they have already been used in previous lines of treatment for relapse.

The chemo or chemo-immunotherapies, with the exception of obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance treatment, are therefore no longer designated as therapy options as part of patient-individual therapy as appropriate comparator therapy.

In addition, newer therapy options were added as part of patient-individual therapy, taking into account the statements of scientific-medical societies in the present benefit assessment procedure.

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

As a result of this change in the appropriate comparator therapy, bendamustine + obinutuzumab followed by obinutuzumab maintenance treatment in accordance with the marketing authorisation, lenalidomide + rituximab, rituximab monotherapy, tisagenlecleucel and mosunetuzumab are considered suitable comparators as part of patient-individual therapy. 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:

Adults with relapsed or refractory (r/r) follicular lymphoma after three or more lines of systemic therapy

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of axicabtagene ciloleucel in patients with relapsed/refractory follicular lymphoma, the pharmaceutical company presented data from the pivotal, single-arm phase II ZUMA-5 study and the retrospective SCHOLAR-5 study.

ZUMA-5 study

The ZUMA-5 study is an ongoing, single-arm, multicentre phase II study investigating the efficacy and safety of axicabtagene ciloleucel in adult patients with indolent non-Hodgkin B-cell lymphoma, with the histological subtype restricted to grade 1, 2 or 3a follicular lymphoma or marginal zone lymphoma (according to WHO classification 2016).

The ZUMA-5 study began in June 2017 and is being conducted at study sites in North America and France.

Patients with histological grade 3b follicular lymphoma or with transformed follicular lymphoma or transformed marginal zone lymphoma were excluded from participation in the study.

Patients had to have refractory or relapsed disease after at least 2 previous therapies, including a monoclonal anti-CD20 agent in combination with an alkylating agent.

Prior to treatment, the study required preparations for the patient-individual production of the CAR-T cell preparation, starting with leukapheresis. The start of leukapheresis was also the time of enrolment in the study. The median time between leukapheresis and infusion for all patients with follicular lymphoma in the ZUMA-5 study was 27 days. During this period, patients could receive anti-cancer therapy to control the disease (bridge therapy) if necessary.

The treatment with axicabtagene ciloleucel was carried out in accordance with the product information. In addition, under certain conditions, a 2nd treatment with axicabtagene ciloleucel was possible.

The primary endpoint of the study is the objective response rate. Secondary endpoints include overall survival and endpoints of side effects.

For the benefit assessment, the pharmaceutical company submits the results of the data cut-off of a 3rd follow-up analysis in month 36 with data cut-off from 31.03.2022. This follow-up analysis is not pre-specified and was conducted when the median follow-up time after

axicabtagene ciloleucel infusion for treated patients with follicular lymphoma had reached 36 months.

For the present benefit assessment, the pharmaceutical company exclusively considered the sub-population of patients with refractory or relapsed follicular lymphoma after 3 or more lines of systemic therapy and accordingly used the data from 75 of the total of 157 patients enrolled in the ZUMA-5 study.

SCHOLAR-5 study

The SCHOLAR-5 study is a retrospective, multicentre study based on electronic patient records, with patients with relapsed or refractory indolent non-Hodgkin lymphoma. Patients with relapsed or refractory (grade 1-3a) follicular lymphoma or marginal zone lymphoma who had received 2 or more prior lines of therapy were enrolled.

With this study, an external comparator group (SCHOLAR-5 cohort) will be formed, which should be comparable to the patient population of the single-arm ZUMA-5 study on axicabtagene ciloleucel in terms of disease characteristics.

For the SCHOLAR-5 study, data on patients with relapsed or refractory indolent non-Hodgkin lymphoma from oncological practices in the USA, the United Kingdom, France and Spain who were treated outside of a clinical study were collected in accordance with the study protocol.

For the SCHOLAR-5 cohort, the pharmaceutical company used data from several data sources. These are data from the two databases IQVIA and Vanderbilt University Medical Centre as well as data from the DELTA study.

For the present benefit assessment, the 3 data sources for the control cohort resulted in a total of 82 patients with different therapy options on the side of the appropriate comparator therapy.

The inclusion and exclusion criteria for the SCHOLAR-5 cohort from these data sources are based on selected criteria used in the ZUMA-5 clinical study. Accordingly, patients aged 18 and over with a histologically confirmed diagnosis of indolent non-Hodgkin lymphoma with a histological subtype of grade 1, grade 2 or grade 3a follicular lymphoma or marginal zone lymphoma were considered. The data from patients with marginal zone lymphoma were excluded accordingly. Patients had to have relapsed or refractory disease and commenced at least the 3rd line of therapy. Treatment with an anti-CD20 antibody in combination with alkylating chemotherapy must have already been carried out. According to the ZUMA-5 study, patients with grade 3b follicular lymphoma or transformed follicular lymphoma were excluded.

The data of the SCHOLAR-5 cohort are compared with the data of the patients of the ZUMA-5 study in month 24 (2nd follow-up analysis) and in month 36 (3rd follow-up analysis).

The comparison presented

The pharmaceutical company presents a comparison of individual arms from the studies described in order to derive the additional benefit of axicabtagene ciloleucel compared with the appropriate comparator therapy. On the axicabtagene ciloleucel side, this consists of patient-individual data from the single-arm ZUMA-5 study, and on the comparator side, of patient-individual data from the retrospective SCHOLAR-5 study.

In order to equalise differences between the data from the ZUMA-5 study and the external comparator group, the inclusion and exclusion criteria for the SCHOLAR-5 cohort are based on selected criteria used in the ZUMA-5 clinical study. In addition, the pharmaceutical company carries out a weighted analysis according to a standardised mortality ratio (SMR) weighting.

According to the pharmaceutical company, the use of a propensity score method is intended to ensure that the differences observed between the treatment groups can be attributed to the axicabtagene ciloleucel intervention.

The comparison presented by the pharmaceutical company is unsuitable for deriving an additional benefit of axicabtagene ciloleucel compared with the G-BA's appropriate comparator therapy. This is mainly due to the following points:

Since the necessary structural equality between the treatment groups is not guaranteed in the non-randomised comparison presented, group differences in possible confounders must be taken into account in the estimation. To do this, relevant counfounders must be systematically identified. It must also be ensured that the data set used contains the necessary information on the identified confounders. Subsequently, any risk of bias posed by the confounders must be adequately taken into account using suitable adjustment methods. A total of 20 out of 26 variables were pre-specified to be used for the propensity score estimation model. These include the variables Follicular Lymphoma International Prognostic Index (FLIPI) total score and bone marrow involvement, the importance of which was rated as high and medium respectively by clinical experts. According to the pharmaceutical company, these variables are not part of the list of variables for determining the propensity scores due to the high percentage of missing data in the data sources used for the SCHOLAR 5 cohort and are therefore not included in the final selection of variables for the propensity score estimation model. Due to the lack of inclusion of these variables considered relevant by clinical experts, it remains uncertain what influence the lack of information on relevant confounders may have on the certainty of the results of the observed effects on overall survival of the SCHOLAR-5 cohort. The G-BA sees the lack of inclusion of these variables, which are estimated to be relevant, and the resulting uncertainties for the estimate of overall survival as a major reason for the unsuitability of the comparison presented. In addition, the study protocol did not describe how the original list of 26 variables was selected. In total, only 9 potential confounders were included in the propensity score model. It is not clear from the information provided by the pharmaceutical company how the reduction in confounders was achieved as the information provided in this regard varies or is not detailed enough.

In conclusion, the indirect comparison presented is unsuitable for the benefit assessment of axicabtagene ciloleucel, particularly due to the questionable structural similarity between the treatment arms and the lack of systematic identification of potential confounders.

In addition, further uncertainties arise from the following points of criticism:

Comparator data on patient-relevant endpoints were only presented for the endpoint of overall survival.

Furthermore, no comparative results on adverse events are available as these were recorded in the ZUMA-5 study, but not in the SCHOLAR-5 cohort. It is therefore not possible to perform a complete benefit-risk assessment for axicabtagene ciloleucel on the basis of the comparison presented.

It should also be critically noted that for the 82 patients in the final SCHOLAR 5 cohort considered in the analysis, for the most part only information on product classes and not on the specific active ingredients used is available with regard to the comparator therapies used in each case. In addition, the therapy options used include a larger percentage of experimental therapies. It is therefore not possible to assess whether the appropriate comparator therapy determined by the G-BA was implemented.

Overall assessment

For the assessment of the additional benefit of axicabtagene ciloleucel in patients with relapsed or refractory follicular lymphoma after three or more lines of systemic therapy, the pharmaceutical company presented a comparison of individual arms from different studies, consisting of patient-individual data from the pivotal, single-arm phase II ZUMA-5 study (intervention side) and patient-individual data from the retrospective SCHOLAR-5 study (comparator side).

The presented comparison of individual arms from the ZUMA-5 and SCHOLAR-5 studies is unsuitable for the benefit assessment of axicabtagene ciloleucel, particularly due to the questionable structural similarity between the treatment arms and the lack of systematic identification of potential confounders.

Thus, no suitable data are available to enable an assessment of the additional benefit, which is why an additional benefit of axicabtagene ciloleucel in patients with relapsed or refractory follicular lymphoma after three 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 the benefit assessment of a new therapeutic indication for the active ingredient axicabtagene ciloleucel. Axicabtagene ciloleucel was approved as an orphan drug. Because of exceeding the EUR 30 million turnover limit for axicabtagene ciloleucel in accordance with Section 35a, para. 1, sentence 12 SGB V, a regular assessment for the new therapeutic indication is carried out accordingly.

The therapeutic indication assessed here is "Treatment of adult patients with relapsed/refractory follicular lymphoma (FL) after three or more lines of systemic therapy".

For these patients, a patient-individual therapy was determined as an appropriate comparator therapy by selecting bendamustine + obinutuzumab followed by obinutuzumab maintenance treatment in accordance with the marketing authorisation, lenalidomide + rituximab, rituximab monotherapy, mosunetuzumab and tisagenlecleucel, taking into account the previous therapy, the course of the disease and the general condition.

To demonstrate the additional benefit of axicabtagene ciloleucel, the pharmaceutical company presents a comparison of individual arms from different studies, consisting of patient-individual data from the pivotal, single-arm phase II ZUMA-5 study (intervention side) and patient-individual data from the retrospective SCHOLAR-5 study (comparator side).

The presented comparison of individual arms from the ZUMA-5 and SCHOLAR-5 studies is unsuitable for the benefit assessment of axicabtagene ciloleucel, particularly due to the questionable structural similarity between the treatment arms and the lack of systematic identification of potential confounders.

Thus, no suitable data are available to enable an assessment of the additional benefit, which is why an additional benefit of axicabtagene ciloleucel in patients with relapsed or refractory follicular lymphoma after three or more lines of systemic therapy is not proven.

The resolution is limited till 1 July 2024 to enable 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.

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 the patient numbers provided by the pharmaceutical company. This information provided by the pharmaceutical company is fraught with uncertainties. The main reasons for this are uncertainties in the derivation of the prevalence of follicular lymphoma and the limited transferability of percentage values for lines of therapy from the studies used by the pharmaceutical company to the prevalence.

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: 20 September 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).

Patients with grade 3b follicular lymphoma were not investigated in the ZUMA-5 study. Grade 3b follicular lymphoma is treated in accordance with the generally accepted state of medical knowledge, analogous to diffuse large B-cell lymphoma (DLBCL). Axicabtagene ciloleucel has a separate marketing authorisation for the treatment of patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

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 were used as the calculation basis.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

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.

As it is not always possible to achieve the exact target dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

In the present therapeutic indication, the product information for obinutuzumab specifies an induction regimen in combination with bendamustine over 6 cycles of 28 days each. Section 5.1 of the product information for obinutuzumab specifies the dose for bendamustine (in combination with obinutuzumab) as 90 mg/m^2. The induction phase is followed by

obinutuzumab monotherapy as maintenance treatment once every 2 months for a period of 2 years or until disease progression.

The product information for mosunetuzumab for this therapeutic indication provides for a therapy over 8 cycles of 21 days each, whereby no further treatment cycles are required for patients who show a complete response (CR) after the 8 cycles. Patients who show a partial response (PR) after the 8 cycles are additionally given 9 cycles of treatment (17 cycles in total).

CAR-T cell therapies

Axicabtagene ciloleucel and tisagenlecleucel 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 as treatment options of the appropriate comparator therapy.

Axicabtagene ciloleucel and tisagenlecleucel are listed on LAUER-TAXE®, but are only dispensed to appropriately qualified inpatient treatment centres. 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 and tisagenlecleucel are administered as a single intravenous infusion according to the requirements in the underlying product information.

Treatment period:

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				
Bendamustine + obinutuzumab				
Bendamustine	Induction therapy: Day 1 and 2 of a 28-day cycle	6	2	12
Obinutuzumab	Induction therapy: 28-day cycles; Cycle 1: Day 1, 8 and 15 Cycles 2 to 6: Day 1	6	Cycle 1: 3 Cycle 2 - 6: 1	8
	Maintenance treatment: every 56 days	3	1	3
Lenalidomide + rituximab				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Lenalidomide	Day 1 - 21 of a 28-day cycle	12	21	252
Rituximab	<u>Induction therapy:</u> Day 1, 8, 15 and 22 of a 28-day cycle	1	4	4
	<u>Maintenance treatment:</u> Day 1 of a 28-day cycle	4	1	4
Rituximab monotherapy				
Rituximab	1 × weekly for 4 weeks	4	1	4
Tisagenlecleucel				
Tisagenlecleucel	Single dose	1	1	1
Mosunetuzumab				
Mosunetuzumab	<u>Cycle 1:</u> Day 1, 8 and 15 of a 21-day cycle <u>Cycle 2:</u> Day 1 of a 21-day cycle <u>From cycle 3 onwards:</u> Day 1 of a 21-day cycle	8 - 17	<u>Cycle 1:</u> 3 <u>From cycle 2 onwards:</u> 1	10 - 19

<u>Consumption:</u>

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).[4]

The consumption of vials and infusion bags is presented for axicabtagene ciloleucel and tisagenlecleucel 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 are independent of the specific number of vials or infusion bags used.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	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/kg CAR+ T cells	1 single infusion bag	1	1 single infusion bag

4 Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	1 - 2 x 10^6 viable CAR+ T cells per kg				
	≥ 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					
Bendamustine + obinutuzumab					
Bendamustine	90 mg/m² = 171 mg	171 mg	1 x 100 mg + 3 x 25 mg	12	12 x 100 mg + 36 x 25 mg
Obinutuzumab	1,000 mg	1,000 mg	1 x 1,000 mg	11	11 x 1,000 mg
Lenalidomide + rituximab					
Lenalidomide	20 mg	20 mg	1 x 20 mg	252	252 x 20 mg
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	8	8 x 500 mg + 24 x 100 mg
Rituximab monotherapy					
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg + 3 x 100 mg	4	4 x 500 mg + 12 x 100 mg
Tisagenlecleucel					
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
Mosunetuzumab					
Mosunetuzumab	<u>Cycle 1:</u> Day 1: 1 mg Day 8: 2 mg Day 15: 60 mg	<u>Cycle 1:</u> Day 1: 1 mg Day 8: 2 mg Day 15: 60 mg	<u>Cycle 1:</u> Day 1: 1 mg Day 8: 2 x 1 mg Day 15: 2 x 30 mg	10 - 19	3 x 1 mg + 10 x 30 mg – 3 x 1 mg + 19 x 30 mg
	<u>Cycle 2:</u> Day 1: 60 mg	<u>Cycle 2:</u> Day 1: 60 mg	<u>Cycle 2:</u> Day 1: 2 x 30 mg		

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	From cycle 3 onwards: Day 1: 30 mg	From cycle 3 onwards: Day 1: 30 mg	From cycle 3 onwards: Day 1: 1 x 30 mg		

Costs:

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

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	€ 272,000.00	€ 0[5]	€ 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					
Rituximab 500 mg	2 CIS	€ 3,639.53	€ 2.00	€ 350.68	€ 3,286.85
Rituximab 100 mg	2 CIS	€ 748.12	€ 2.00	€ 69.93	€ 676.19
Bendamustine 100 mg	5 PIC	€ 1,620.96	€ 2.00	€ 204.07	€ 1,414.89
Bendamustine 100 mg	1 PIC	€ 331.03	€ 2.00	€ 40.46	€ 288.57
Bendamustine 25 mg	5 PIC	€ 414.43	€ 2.00	€ 51.01	€ 361.42
Bendamustine 25 mg	1 PIC	€ 99.39	€ 2.00	€ 11.15	€ 86.24
Obinutuzumab 1,000 mg	1 PIC	€ 2,649.25	€ 2.00	€ 253.73	€ 2,393.52
Lenalidomide 20 mg	63 HC	€ 117.32	€ 2.00	€ 8.38	€ 106.94
Mosunetuzumab 1 mg	1 CIS	€ 275.87	€ 2.00	€ 25.11	€ 248.76
Mosunetuzumab 30 mg	1 CIS	€ 7,751.61	€ 2.00	€ 753.26	€ 6,996.35
CAR-T cells					

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

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[5]	€ 239,000.00

Abbreviations:
HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; PSI = powder for solution for injection, PIC = powder for the preparation of an infusion solution concentrate; DSS = dry substance without solvent

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 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.

Conditioning chemotherapy for lymphocyte depletion under CAR-T cell therapy

Axicabtagene ciloleucel 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 Medicinal Products Act, no further costs are incurred in this respect for the medicinal product to be assessed and the mentioned active ingredients of the appropriate comparator therapy.

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 6 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 or tisagenlecleucel. This test is not required for all therapy options of the appropriate comparator therapy. Since there is a regular difference between the medicinal product to be assessed and the appropriate comparator therapy with regard to the tests for hepatitis B, hepatitis C and HIV, the costs of additionally required SHI services are presented in the resolution.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed							
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
Screening for HBV, HCV and HIV							
Hepatitis-B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Hepatitis C HCV antibody status (GOP: 32618)	-	-	-	-	€ 9.80	1.0	€ 9.80
HIV HIV-1 and HIV-2 antibody status (GOP: 32575)	-	-	-	-	€ 4.45	1.0	€ 4.45
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
Screening for HBV, HCV and HIV							
Hepatitis-B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Hepatitis C HCV antibody status (GOP: 32618)	-	-	-	-	€ 9.80	1.0	€ 9.80
HIV HIV-1 and HIV-2 antibody status (GOP: 32575)	-	-	-	-	€ 4.45	1.0	€ 4.45
Bendamustine + obinutuzumab followed by obinutuzumab maintenance treatment							

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
HBV diagnostics							
HBV test Hepatitis B surface antigen status (GOP number 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Hepatitis-B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Rituximab							
Premedication for rituximab monotherapy							
Dimetindene (1 mg/10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.53	€ 16.19	4.0	€ 32.38
Paracetamol[9] (500 mg - 1,000 mg, PO)	10 TAB at 500 mg – 10 TAB at 1,000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	4.0	€ 2.68 – € 3.01
HBV diagnostics							
HBV test Hepatitis B surface antigen status (GOP number 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Hepatitis-B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Premedication for rituximab + lenalidomide							
Dimetindene (1 mg/10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.53	€ 16.19	8.0	€ 64.76
Paracetamol[9] (500 mg - 1,000 mg, PO)	10 TAB at 500 mg – 10 TAB at 1,000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	8.0	€ 2.68 – € 3.01
HBV diagnostics							
HBV test Hepatitis B surface antigen status (GOP number 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Hepatitis-B HBV antibody status (GOP: 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Mosunetuzumab							
Premedication for the first two cycles							
Dimetindene (1 mg/10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.53	€ 16.19	4.0	€ 32.38
Paracetamol[9] (500 mg - 1,000 mg, PO)	10 TAB at 500 mg – 10 TAB at 1,000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	4.0	€ 2.68 – € 3.01
Dexamethasone[9] (20 mg, IV)	10 AMP at 4 mg	€ 16.92	€ 2.00	€ 0.36	€ 14.56	4.0	€ 28.96
Abbreviations: SFI = solution for injection; INF = infusion solution; CII = concentrate for injection or infusion solution; TAB = tablets; 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 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

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

Basic principles of the assessed medicinal product

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

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

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

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

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

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

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or

- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient:

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

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

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

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

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

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

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

Designation

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

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

Exception to the designation

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

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

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGBV.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with relapsed or refractory (r/r) follicular lymphoma after three or more lines of systemic 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: 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 Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 23 May 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 2 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 28 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
Subcommittee Medicinal products	23 May 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	31 October 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 the Pharmaceuticals Directive

Berlin, 21 December 2023

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

Prof. Hecken