Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an amendment to the Pharmaceuticals Directive (AM-RL): Annex XII – Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V Axicabtagene ciloleucel

From 2 May 2019

Contents

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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 for the treatment of a rare condition (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999, the additional medical benefit is deemed to be proven through the grant of market authorisation according to Section 35a paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy need not be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an evaluation of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, Nos. 2 and 3 SGB V in conjunction with the 5th Chapter Sections 5 et seq. of the Rules of Procedure of the G-BA (VerfO) has not been carried out. Only the extent of the additional benefit must be demonstrated.

However, the restricted benefit assessments for orphan drugs as linked by law to marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices including VAT exceeds €50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical manufacturer must, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5 Section 5, subsections 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO. In this dossier, the pharmaceutical manufacturer must also provide evidence of the additional benefit in relation to the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG; Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen). On the basis of the statutory requirement in Section 35a paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at its meeting on 15 March 2012 to the effect that, in the case of orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided by the G-BA is assessed exclusively on the basis of the approval studies.

Accordingly, at its meeting on 15 March 2012, the G-BA amended the mandate given to the IQWiG by resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V in such a way that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the drug concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA 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 shall decide on the benefit assessment within three months of its publication. The resolution is to be published on the Internet and forms part of the Pharmaceuticals Directive.

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2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient axicabtagene ciloleucel in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is the 1 November 2018. The pharmaceutical manufacturer has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 1 VerfO on 31 Oktober 2018 .

Axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) is authorised as a medicinal product for the treatment of a rare condition under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999.

In accordance with Section 35a paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is deemed to be proven through the grant of market authorisation. The extent of the additional benefit is assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical manufacturer in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 Februar 2019 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de) , thus initiating the written statement procedure. An oral hearing was also held.

The G-BA has made its resolution on the basis of the dossier of the pharmaceutical manufacturer, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G18-18) prepared by the IQWiG, and the statements submitted in the written and oral hearing procedure as well as the amendment to the benefit assessment prepared by the G-BA.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 1, sentence 1, numbers 1–4 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 comments received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of axicabtagene ciloleucel (YESCARTA®) in accordance with the product information

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

[1] General methods, Version 5.0 from 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

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2.1.2 Extent of the additional benefit

a) Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more systemic therapies

and

b) Adult patients with relapsed or refractory primary mediastinal large B-cell lymphoma (PMBCL) after two or more systemic therapies

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

Axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primarily mediastinal large B-cell lymphoma (PMBCL) after two or more systemic therapies has a non-quantifiable additional benefit.

Grounds:

To determine the extent of the additional benefit of axicabtagene ciloleucel (Axi-Cel) for the treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) after two systemic therapies, the results of the ZUMA-1 single-arm pivotal phase I/II study, the SCHOLAR-1 retrospective study, and the NCI 09-C-0082 supportive phase I study as well as indirect comparisons with other historical controls are available.

The NCI 09-C-0082 study

The NCI 09-C-0082 supportive study is an open, single-arm phase I dose-finding study. In the study, the manufacturing process of Axi-Cel was varied, and various doses of lymphocyte-depleting chemotherapy, most of which do not conform to regulatory requirements, were investigated. The study is therefore not used for the benefit assessment.

ZUMA-1 study

The ZUMA-1 study is a single-arm, multi-centre Phase I/II study to evaluate the efficacy and safety of Axi-Cel in patients with chemotherapy-refractory DLBCL (including the subtype transformed follicular lymphoma (TFL)) and primarily mediastinal large B-cell lymphoma (PMBCL). The study participants had to show a chemorefractory disease according to the criteria defined in the study: progressive disease as best response to first-line therapy or stable disease as best response after at least four cycles of first-line chemotherapy; progressive disease as best response to last-line chemotherapy or stable disease as best response after at least two cycles of last-line chemotherapy; refractory after autologous stem cell transplantation (disease progression or relapse within 12 months after transplantation). In addition, patients must have received prior therapy with an anti-CD20 antibody and anthracycline-based chemotherapy.

The study contains three patient cohorts. Cohort 1 included patients with DLBCL, and Cohort 2 included patients with TFL and PMBCL. In Cohort 3, the prophylactic administration of tocilizumab and levetiracetam in patients with relapsed or refractory DLBCL, TFL, and PMBCL is investigated. Because this does not currently constitute an intervention in conformity with the authorisation, Cohort 3 is not taken into account for the benefit assessment. Because the present study on Axi-Cel is an open-label and non-randomised phase II study, in principle, a high potential for distortion for all endpoints must be assumed.

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In Phase I, a total of eight patients with r/r DLBCL were enrolled to investigate the incidence of adverse events (AEs) and dose-limiting toxicity (DLT) for both lymphocyte-depleting chemotherapy and Axi-Cel. One patient could not receive treatment with Axi-Cel because of disease progression. Thus, a total of seven patients in Phase I were infused with Axi-Cel.

A total of 111 patients were included in Phase II, including 81 patients with DLBCL, 21 patients with TFL, and 9 patients with PMBCL. In the ZUMA-1 study, this patient population is referred to as the FAS population and corresponds to the ITT principle. The median time from inclusion, which corresponds to the time of leukapheresis, to infusion of Axi-Cel was 23 days for patients with DLBCL, 22 days for patients with TFL, and 23.5 days for patients with PMBCL. Of the patients included, 4 patients with DLBCL, 5 patients with TFL, and 1 patient with PMBCL dropped out of the study before receiving the infusion of Axi-Cel. The main reasons were adverse events and death. Thus, a total of 101 patients in Phase II were infused with Axi-Cel (mITT population).

No patient received additional anti-neoplastic chemotherapy to bridge the period until Axi-Cel was available. Lymphocyte-depleting chemotherapy was initiated on the 5th day prior to Axi-Cel infusion and was administered to almost all patients in the form of fludarabine and cyclophosphamide.

After lymphocyte-depleting chemotherapy, patients were hospitalised for infusion of Axi-Cel. Axi-Cel was administered in a single infusion. In the case of cytokine release syndrome (CRS) or neurological events, the administration of tocilizumab, corticosteroids, and other immunosuppressants (CRS only) was permitted as concomitant medication. Hospitalisation was to continue for another 7 days after infusion, and discharge was usually only possible after all non-haematological toxicities related to Axi-Cel had subsided (Grade ≤ 1). The median hospitalisation was 15 days for patients with DLBCL and 14.5 days for patients with TFL and PMBCL. The post-treatment follow-up was planned between Study week 2 and Study month 3 after which the long-term follow-up up to Month 24 and the subsequent survival follow-up up to the end of the study are planned (maximum 15 years).

Information on anti-neoplastic therapies in patients who were progressive after the infusion of Axi-Cel is not available. However, according to the study documents, patients who showed a complete or partial response at Month 3 could receive re-treatment with Axi-Cel under certain criteria. Re-therapy with Axi-Cel was limited to a maximum of one new infusion. In total, 9 patients with DLBCL, 1 patient with TFL, and 1 patient with PMBCL received re-treatment with Axi-Cel. Furthermore, the study documents show that 4 patients of Cohort 1 and 2 patients of Cohort 2 were censored for the analysis of progression-free survival (PFS) on the basis of a stem cell transplantation (SCT).

Relative to the FAS population, the patients had a median age of 58 years (DLBCL), 63 years (TFL), and 32 years (PMBCL). All patients had an ECOG performance status of 0-1. Most patients were in disease stage III or IV and showed no B symptoms upon study inclusion. > 70% of patients with TFL, > 80% of patients with DLBCL, and > 50% of patients with PMBCL had ≥ 2 risk factors according to the “International Prognostic Index (IPI)”. The majority of patients were refractory to at least two lines of therapy and had not received autologous SCT as pre-therapy. The characteristics between FAS and mITT population for patients with DLBCL, TFL, and PMBCL are largely comparable.

Inherent components of treatment with Axi-Cel are leukapheresis, waiting time until manufacture of the product, and lymphocyte-depleting chemotherapy. The influence of

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these components on the treatment of patients with Axi-Cel in the clinical care context can be adequately mapped only by considering the ITT population. In the ZUMA-1 study, only a few patients were eliminated before receiving the infusion of Axi-Cel. The patient characteristics between the FAS and mITT populations are also largely comparable. Because of the aspects described, the FAS population is used as the relevant analysis population for the present assessment of Axi-Cel.

The study is currently being conducted at 24 study centres in the US and in Israel. In the initial dossier, the pharmaceutical manufacturer presents the data of the a priori planned primary analysis as well as the post hoc update analysis of 11 August 2017 in which the patients were followed up for 12 months. The data cut-off of 11 August 2017 for the ZUMA-1 study was the basis for the marketing authorisation. However, for essential information on the course of the study and on study results for the lymphoma subentities TFL and PMBCL, there are no separate evaluations available for this data cut-off in relation to the FAS population. With the written statement, the pharmaceutical manufacturer submits the data of the update analysis with 24 months follow-up (data cut-off of 11 August 2018) for the purpose of inclusion in the benefit assessment. According to the pharmaceutical manufacturer, these data were available only after submission of the benefit assessment dossier on 31 October 2018. More comprehensive evaluations of the individual lymphoma subentities related to the FAS population are available for this data cut-off. In addition, according to the EPAR[2], this data cut-off will be made available to the European Medicines Agency to assess the durability of the effects of Axi-Cel as part of the risk minimisation measures. For the present benefit assessment, the data cut-off of 11 August 2018 is therefore used to assess the extent of the additional benefit of Axi-Cel, taking into account the longer observation period and the more comprehensive evaluations of the individual lymphoma subentities relevant for the benefit assessment.

According to the EPAR[2], patients with DLBCL, TFL, and PMBCL are similar with respect to the pathogenesis, treatment, and prognosis of the disease. Furthermore, the ZUMA-1 study shows similar results for patients with DLBCL, TFL, and PMBCL. Because patients with PMBCL account for only about 8% of the total population of the ZUMA-1 study, the G-BA also considers the results of the total population to be representative for patients with DLBCL or TFL. In addition to the individual results of Cohorts 1 and 2, the overall results of the ZUMA-1 study were used by the European Medicines Agency to assess the benefit-risk ratio of Axi-Cel for patients with both r/r DLBCL and r/r PMBCL during the approval process[2]. Taking into account the aspects described above and the rarity of the lymphoma subentity PMBCL, in the present assessment, the overall results of the ZUMA-1 study, which include all three lymphoma subentities, are therefore also considered when assessing the extent of the additional benefit for the patient population with r/r DLBCL as well as with r/r PMBCL.

Historical comparisons

For the efficacy endpoints of the ZUMA-1 study, the pharmaceutical manufacturer presents indirect historical comparisons with the retrospective SCHOLAR-1 study and 15 published studies. The pharmaceutical manufacturer does not differentiate according to lymphoma subentity (DLBCL or PMBCL).

2 European Public Assessment Report (EPAR) - YESCARTA® (22 June 2018)

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About the SCHOLAR-1 study

The SCHOLAR-1 study is an international, retrospective study, which includes patient data from a total of four studies.

The data of the "MD Anderson Cancer Center (MDACC)" study and the study of the "Specialized Program of Research Excellence (SPORE)" of the Mayo Clinic and University of Iowa (MC/IA) were obtained from observation studies. Patients with r/r DLBCL and TFL after two preceding therapy lines were included in the MDACC study. The preceding therapy lines had to include a chemotherapy containing rituximab and a platinum-based salvage chemotherapy. In the MC/IA study, patients with newly diagnosed lymphoma were included and their treatment or, respectively, disease status was documented prospectively.

In addition, the SCHOLAR-1 study includes data from the follow-up phase of two randomised, controlled phase III studies. In the LY.12 study of the National Cancer Institute of Canada (NCIC) Cancer Trials Group (CTG), patients with a relapse after a chemotherapy containing an anthracycline were included. The study medication consisted of two different salvage chemotherapy regimens. The phase III CORAL study (Collaborative Trial in Relapsed Aggressive Lymphoma) of the French Lymphoma Academic Research Organization (LYSARC) includes patients with a primary relapsed DLBCL after a chemotherapy containing an anthracycline. The study medication in this study also consisted of two different salvage chemotherapy regimens with the aim of subsequently performing a consolidating autologous SCT. After the SCT, the participants were further randomised for follow-up observation or maintenance therapy with rituximab.

For the indirect historical comparison, patient-specific data from the SCHOLAR-1 study were available to the pharmaceutical manufacturer. The inclusion criteria for the historical comparison were the determination of a refractory disease status and the maintenance of a follow-up therapy for the treatment of the refractory disease. Two analysis populations were defined depending on the refractory status: "first refractory" and "last refractory". The "first refractory" population is based on the first time in the course of treatment when the patient was classified as refractory. In contrast, the "last refractory" population, is based on the last time when the patient's refractory status was determined in the course of treatment. Because fewer patients received follow-up therapy for the treatment of the most recently diagnosed refractory disease at this later point in time, the analysis population in the "last refractory" set is smaller than in the "first refractory" set. The "last refractory" analysis population is more comparable with the inclusion and exclusion criteria of the ZUMA-1 study (which also focus on refractoriness on later lines of therapy) than the "first refractory" population.

In the dossier, the pharmaceutical manufacturer refers to the "first refractory" analysis population of the SCHOLAR-1 study (n = 636). It presents the patient characteristics for the analysis population with exclusion of primary refractory patients not included in the therapeutic indication of Axi-Cel (n = 456). For the overall survival analysis, the manufacturer states that n = 424 patients have a documented survival status. For the specifically selected patient populations for the overall survival analysis, the pharmaceutical manufacturer does not present any patient characteristics, so that comparability with the ZUMA-1 study cannot be assessed. In addition, the pharmaceutical manufacturer only analyses the SCHOLAR-1 study versus the mITT population of the ZUMA-1 study.

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With the written statement, the pharmaceutical manufacturer submits a new indirect comparison to the SCHOLAR-1 study using the 24-month data of the ZUMA-1 study (data cut-off of 11 August 2018). This also takes into account the ITT population (FAS population) of the ZUMA-1 study. However, based on the written statement, the selection process of the specific comparison population for the overall survival analysis could not be traced. There were also no patient characteristics for the specifically selected patient populations of the SCHOLAR-1 study. This information was provided by the pharmaceutical manufacturer following the oral hearing.

The newly performed indirect comparison is based on the “last refractory” analysis population (n= 593). The pharmaceutical manufacturer excludes patients with primary refractory disease and a documented ECOG status of > 1; this results in a population of n = 416. Patients with unevaluated or unknown ECOG status are still included in the analysis. Based on the documentation submitted, it cannot be assessed whether the number of excluded patients with ECOG > 1 and primary refractory disease is correct.

For the analysis of overall survival, the pharmaceutical manufacturer includes only patients with a documented survival status at the last follow-up. In accordance with the above, for the purposes of this assessment, the evaluation taking into account the ITT population (n = 390) is also considered decisive for the indirect comparison. Patient characteristics are available for this specifically selected patient population.

Overall, when looking at the patient characteristics, it can be seen that the patients in the ZUMA-1 study were 4 years older (median). A larger percentage of patients have ≥ 3 risk factors (in accordance with IPI), a more advanced disease stage, and a larger number of previous lines of therapy. Uncertainties arise because for the “last refractory” patient population of the SCHOLAR-1 study, ECOG status, IPI value, and disease stage were not assessed in a large proportion of the patients. However, in view of the advanced treatment situation after at least two systemic pre-therapies, taking into account the assessment presented by medical societies in the present benefit assessment procedure, the prognostic significance of these factors cannot be conclusively assessed. Uncertainties also arise because of a possible selection effect through the selection of the assessable population of the SCHOLAR-1 study and through the historically and temporally different collection of the data of the SCHOLAR-1 study compared with the ZUMA-1 study.

Despite the uncertainties and possible differences between the patient populations, the present indirect historical comparison with the SCHOLAR-1 study is considered sufficiently valid for the assessment of the extent of the additional benefit, taking into account the inconclusively assessable prognostic significance of the ECOG status, the IPI value, and the disease stage for the further course of therapy in the present treatment situation as well as the advanced, predominantly deterministic disease state of the patient population examined here.

About the 15 published studies

The indirect historical comparison with 15 published studies was performed by the pharmaceutical manufacturer using a meta-analytical model with fixed and random effects, whereby the pharmaceutical manufacturer only considered the data of the mITT population of the ZUMA-1 study. The comparative populations comprise six studies with data on medicinal products previously approved in Germany and nine studies with data on allogeneic SCT.

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Of the six studies with data on medicinal products previously approved in Germany, data on patient characteristics are only available for the patient population of the study by Eyre et al. (2016) in which the total population is taken into account in the indirect comparison. Relevant differences of the patient characteristics in comparison to the ZUMA-1 study (e.g. with regard to the age of the patients) were found. Of the further five studies with data on medicinal products previously approved in Germany, only sub-populations were selected for indirect comparison. No patient characteristics are available for these specifically selected sub-populations; comparability with the ZUMA-1 study can therefore not be assessed.

For the 9 studies with data on allogeneic SCT, information on relevant patient characteristics of the specifically selected comparison populations is equally missing (Armand et al. (2008)), or the comparability of the patient populations is not given, for example because of significant differences in the age of the patients (Avivi et al. (2014); Lazarus et al. (2010); Ghobadi et al. (2015); Rigacci et al. (2012), and von Kampen et al. (2011)). In addition, the characteristic “age” is partly defined differently in the studies than it is in the ZUMA-1 study.

Overall, there are relevant uncertainties because of the lack of information on the patient characteristics or relevant differences between the patient characteristics of the studies. In addition, the indirect comparison with the 15 published studies refers exclusively to the 12-month data of the ZUMA-1 study, whereby sufficiently valid conclusions on the long-term effects of Axi-Cel are not possible. Taking these aspects into account, it cannot be assumed that the present indirect historical comparison can provide a relevant, more far-reaching gain in knowledge in contrast to the indirect comparison assessed as sufficiently valid with the SCHOLAR-1 study. Because of the aspects described, the indirect comparison with the 15 published studies is not used for the benefit assessment.

Extent of the additional benefit

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

Mortality

Overall survival

Relative to the FAS population, patients with DLBCL had a median overall survival of 15.7 months (57% of the patients died). For patients with TFL, median overall survival was not achieved. 43% of the patients with TFL had died at the time of this data cut-off. For patients with PMBCL, median overall survival was not achieved. 33% of the patients had died at the time of this data cut-off.

A median overall survival of 17.4 months is observed for the total population. The Kaplan-Meier estimator (K-M estimator) changes only slightly between Month 18 and Month 24. At Month 24, 47.7% of the patients were still alive.

The indirect comparison with the SCHOLAR-1 study shows a statistically significant advantage in favour of Axi-Cel (hazard ratio = 0.30 [0.22; 0.41], $p < 0.0001$). The 24-month survival rate for patients in the ZUMA-1 study is 50% compared with 14% for patients in the SCHOLAR-1 study. Given the poor prognosis for the further course of the disease and the advanced stage of treatment as well as taking into account the above considerations on comparability of patient populations, this effect is evaluated by the G-BA in such a way that an effect is present but cannot be quantified.

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Thus, because of the high bias potential of an indirect historical comparison and additional uncertainties regarding the comparability of patient populations, the small number of patients, a possible selection effect due to the selection of the assessable population of the SCHOLAR-1 study and the historically and temporally different collection of the data of the SCHOLAR-1 study compared with the ZUMA-1 study, a valid quantification of the extent of the additional benefit for the endpoint overall survival cannot be carried out. This is also in line with the opinions of medical societies in the present benefit assessment procedure according to which the efficacy of Axi-Cel in the strongly pre-treated patient population with few therapy alternatives included here is seen. However, the extent of the additional benefit is considered non-quantifiable against the background of the currently available evidence.

Overall, the endpoint of overall survival is identified as having an additional benefit, the extent of which cannot be quantified.

Morbidity

Progression-free survival (PFS)

The assessment of the progression was carried out on the basis of the IWG criteria according to Cheson et al. of 2007[3]. The assessment was carried out both by the investigator and by a central reviewer.

The results of the central reviewer are used for the present assessment, taking into account the lower bias potential. This does not exclude the use of investigator-based assessments in other cases. For patients with DLBCL (Cohort 1), the median PFS of the FAS population was 7.3 months. For patients with TFL and PMBCL there is no separate evaluation for the PFS.

Relative to the total population of the ZUMA-1 study, the median PFS was 9.5 months. The Kaplan-Meier estimators (K-M estimators) dropped to about 38% by Month 18. For Month 24, there is no or only a very slight change in the K-M estimator. The probability of the patients being free of progression at this time is still 38%.

The endpoint PFS is a combined endpoint of mortality and partial response (PR) or complete response (CR). The endpoint component “mortality” is already collected as an independent endpoint via the endpoint overall survival. For the operationalisation of a progression (in PR) according to the IWG criteria[3] of 2007, only morphological, imaging characteristics of the tumour size or growth are considered. The symptoms perceived by the patient are not taken into account. Taking into account the above mentioned aspects, there are different views within the G-BA regarding the patient relevance of the endpoint PFS.

Because of the single-arm study design, a comparative assessment of the study results on the PFS is not possible.

Objective response rate (ORR)

The objective response rate (ORR) consists of the components complete and partial remission (CR and PR). The assessment of the response was based on the IWG criteria[3]

[3] Cheson et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007; 25(5): 579-586

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of 2007. Achieving a CR is an important prognosis factor and relevant for the therapy decision. A CR associated with a noticeable decrease in disease symptoms for the patient is always regarded as relevant for the patient in the benefit assessment. The IWG criteria[3] used almost exclusively consider morphological, imaging characteristics of tumour size and growth.

The ORR evaluated by the investigator was the primary endpoint of the ZUMA-1 trial. The response rate for patients with DLBCL is 79%. For patients with TFL, it is 76%, and for patients with PMBCL, it is 67%. For the total population, the response was 77%; 55% of patients achieved complete remission.

The ORR was also evaluated by the central reviewer. The response for patients with DLBCL and TFL is 67%; for patients with PMBCL, it is 78%. For the total population, the response was 68%; 50% of patients achieved complete remission.

Because of the single-arm study design, a comparative assessment of the response or the rate of complete remissions is not possible.

Quality of life

Data on patients' quality of life were not collected in the ZUMA-1 study.

Side effects

Phase I of the ZUMA-1 study included the collection of safety data (including dose-limiting toxicity), which was reviewed by an internal review team. On the basis of these data, the team of experts made recommendations for the further procedure in the ZUMA-1 study.

In Phase II of the ZUMA-1 study, up to Study month 3, a complete survey of adverse events (AE) was performed after infusion of Axi-Cel. For the period from Study month 3 to Study month 24 after infusion of Axi-Cel, only targeted AE were recorded (neurological events, haematological events, infections, autoimmune diseases, and secondary malignancies).

An increase in AE (total) is apparent from the time of lymphocyte-depleting chemotherapy. After infusion of Axi-Cel all patients had at least one AE. In particular, the rate of severe AE with CTCAE grades 3–4 and serious AE rose sharply to > 90% and > 40%, respectively, after the infusion of Axi-Cel.

Severe AE (CTCAE grade ≥ 3) with incidence ≥ 5% and > 1 event were most commonly present in the SOC disorders of the blood and lymphatic system. PT encephalopathy in particular was shown to be a serious AE with an incidence of ≥ 5% and > 1 event. With respect to AE of special interest for identified risks with incidence ≥ 5% and > 1 event, for a CTCAE grade ≥ 3, neurological events and various cytopenia in particular were found. A CRS with severity ≥ 3 according to the CRS Grading Scale according to Lee et al. was found in > 10% of patients with DLBCL.

Because of the single-arm study design, a comparative assessment of the results on side effects is not possible.

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Overall assessment

a) Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more systemic therapies

The results of the pivotal single-arm Phase I/II ZUMA-1 trial on mortality, morbidity, and adverse reactions will be used to assess the extent of the additional benefit of axicabtagene ciloleucel (Axi-Cel) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more systemic therapies. In addition, the mortality results from the indirect historical comparison with the retrospective SCHOLAR-1 study are used.

The indirect comparison with the SCHOLAR-1 study shows a statistically significant advantage in favour of Axi-Cel for the overall survival endpoint. Given the poor prognosis for the further course of the disease and the advanced stage of treatment as well as taking into account the above considerations on comparability of patient populations, this effect is evaluated by the G-BA in such a way that an effect is present but cannot be quantified. Accordingly, because of the indirect historical comparison and further relevant uncertainties, a valid quantification of the extent of the effect on overall survival is not possible. Overall, the endpoint of overall survival is identified as having a non-quantifiable additional benefit.

Because of the single-arm study design of the ZUMA-1 study, no comparative assessment is possible for the further endpoints of morbidity and side effects. The patients' quality of life was not collected in the ZUMA-1 study.

Against the background of the advanced disease and treatment stage as well as the poor prognosis for the further course of the disease, in the overall assessment, greater importance is attached to the comparative results of overall survival. As a result, the G-BA classifies the extent of additional benefit of axicabtagene ciloleucel as non-quantifiable because of the limited data based on the criteria in Section 5 paragraph 7 AM-NutzenV taking into account the severity of the disease and the therapeutic objective in the treatment of the disease. In accordance with Section 35a paragraph 1, sentence 11, 1st half of the sentence SGB V, an additional benefit exists but is non-quantifiable because the scientific data basis does not permit this.

b) Adult patients with relapsed or refractory primary mediastinal large B-cell lymphoma (PMBCL) after two or more systemic therapies

The results of the pivotal single-arm Phase I/II ZUMA-1 trial on mortality, morbidity, and adverse reactions will be used to assess the extent of the additional benefit of axicabtagene ciloleucel (Axi-Cel) for the treatment of adult patients with relapsed or refractory primarily mediastinal large B-cell lymphoma (PMBCL) after two or more systemic therapies. In addition, the mortality results from the indirect historical comparison with the retrospective SCHOLAR-1 study are used.

The indirect comparison with the SCHOLAR-1 study shows a statistically significant advantage in favour of Axi-Cel for the overall survival endpoint. Given the poor prognosis for the further course of the disease and the advanced stage of treatment as well as taking into account the above considerations on comparability of patient populations, this effect is evaluated by the G-BA in such a way that an effect is present but cannot be quantified. Accordingly, because of the indirect historical comparison and further relevant uncertainties, a valid quantification of the extent of the effect on overall survival is not

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possible. Overall, the endpoint of overall survival is identified as having a non-quantifiable additional benefit.

Because of the single-arm study design of the ZUMA-1 study, no comparative assessment is possible for the further endpoints of morbidity and side effects. The patients' quality of life was not collected in the ZUMA-1 study.

Against the background of the advanced disease and treatment stage as well as the poor prognosis for the further course of the disease, in the overall assessment, greater importance is attached to the comparative results of overall survival. As a result, the G-BA classifies the extent of additional benefit of axicabtagene ciloleucel as non-quantifiable because of the limited data based on the criteria in Section 5 paragraph 7 AM-NutzenV taking into account the severity of the disease and the therapeutic objective in the treatment of the disease. In accordance with Section 35a paragraph 1, sentence 11, 1st half of the sentence SGB V, an additional benefit exists but is non-quantifiable because the scientific data basis does not permit this.

2.1.3 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 has 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 this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a paragraph 1 SGB V.

Treatment with axicabtagene ciloleucel represents a novel therapeutic approach, the long-term effects of which cannot be fully assessed at present, particularly with regard to a potential cure of the patients. The purpose of the present limitation is to provide further evidence on the long-term effects of Axi-Cel on patient-relevant endpoints, which could possibly answer the question of a potential cure of patients, to be included in the benefit assessment.

Conditions of the limitation

For the re-assessment of the benefit, the results of the ZUMA-1 study after 60 months (5 years) should be submitted in the form of a report that fully reflects data on all patient-relevant endpoints, patient characteristics, patient flow, and study outcome for the FAS population.

With regard to an indirect comparison, it should be examined and explained to what extent an indirect comparison with the 60-month data of the ZUMA-1 study can be used, also taking into account any data and information situation that may have developed in the meantime.

In addition, it should be examined and explained to what extent prospective comparative evidence beyond the study justifying the marketing authorisation is available or can be generated for the reassessment of benefit (e.g. also from observational studies), which could contribute to a relevant further knowledge gain for the benefit assessment and could, for example, provide information on administered follow-up therapies after application of Axi-Cel.

For this purpose, the G-BA considers a limitation of the resolution until 15 May 2022 to be appropriate.

In principle, an extension may be granted if it is justified and clearly demonstrated that the period of the limitation is not sufficient.

In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of axicabtagene

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ciloleucel begins again when the deadline has expired. For this purpose, the pharmaceutical manufacturer must submit a dossier to the G-BA at the latest on the day of expiry of the deadline 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).

The possibility that a benefit assessment for axicabtagene ciloleucel can be carried out at an earlier point in time for other reasons (cf. Chapter 5, Section 1 paragraph 2, Nos. 2 – 6 VerfO) remains unaffected by this.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of the medicinal product YESCARTA® with the new active ingredient axicabtagene ciloleucel (Axi-Cel). Axi-Cel has been granted marketing authorisation as an orphan drug. The present assessment refers to the therapeutic indication "YESCARTA is used in the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) after two or more systemic therapies". Therefore, two patient groups were distinguished in the therapeutic indication under consideration:

a) Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more systemic therapies

b) Adult patients with relapsed or refractory primary mediastinal large B-cell lymphoma (PMBCL) after two or more systemic therapies

About patient group a)

The pharmaceutical manufacturer presents the study results of the ZUMA-1 single-arm phase I/II study, the SCHOLAR-1 retrospective study, and the NCI 09-C-0082 supportive phase I study as well as non-adjusted indirect comparisons compared to 15 published studies.

The results of the pivotal single-arm phase I/II study ZUMA-1 on mortality, morbidity, and adverse events will be used to assess the extent of the additional benefit. In addition, the mortality results from the indirect historical comparison with the retrospective SCHOLAR-1 study are used.

The comparison with the SCHOLAR-1 study shows a statistically significant advantage in favour of Axi-Cel for the overall survival endpoint. However, because of the indirect historical comparison and further relevant uncertainties, a valid quantification of the extent of the effect on overall survival is not possible. Overall, the endpoint of overall survival is identified as having a non-quantifiable additional benefit. Because of the single-arm study design of the ZUMA-1 study, no comparative assessment is possible for the further endpoints of morbidity and side effects. The patients' quality of life was not collected in the ZUMA-1 study. Against the background of the advanced disease and treatment stage as well as the poor prognosis for the further course of the disease, in the overall assessment, greater importance is attached to the comparative results of overall survival.

The overall picture shows a non-quantifiable additional benefit.

For this patient population, the resolution will expire on 15 May 2022. The conditions for a time limit include the submission of the 60-month data of the ZUMA-1 study, the examination and presentation of any data and information that may have evolved in the meantime for an indirect comparison of these data, and prospective comparative evidence on axicabtagene ciloleucel

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(e.g. from observational studies) that goes beyond the evidence supporting the marketing authorisation.

About patient group b)

The pharmaceutical manufacturer presents the study results of the ZUMA-1 single-arm phase I/II study, the SCHOLAR-1 retrospective study, and the NCI 09-C-0082 supportive phase I study as well as non-adjusted indirect comparisons compared to 15 published studies.

The results of the pivotal single-arm phase I/II study ZUMA-1 on mortality, morbidity, and adverse events will be used to assess the extent of the additional benefit. In addition, the mortality results from the indirect historical comparison with the retrospective SCHOLAR-1 study are used.

The comparison with the SCHOLAR-1 study shows a statistically significant advantage in favour of Axi-Cel for the overall survival endpoint. However, because of the indirect historical comparison and further relevant uncertainties, a valid quantification of the extent of the effect on overall survival is not possible. Overall, the endpoint of overall survival is identified as having a non-quantifiable additional benefit. Because of the single-arm study design of the ZUMA-1 study, no comparative assessment is possible for the further endpoints of morbidity and side effects. The patients' quality of life was not collected in the ZUMA-1 study. Against the background of the advanced disease and treatment stage as well as the poor prognosis for the further course of the disease, in the overall assessment, greater importance is attached to the comparative results of overall survival.

The overall picture shows a non-quantifiable additional benefit.

For this patient population, the resolution will expire on 15 May 2022. The conditions for a time limit include the submission of the 60-month data of the ZUMA-1 study, the examination and presentation of any data and information that may have evolved in the meantime for an indirect comparison of these data, and prospective comparative evidence on axicabtagene ciloleucel (e.g. from observational studies) that goes beyond the evidence supporting the marketing authorisation.

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2.2 Number of patients and/or demarcation of patient group eligible for treatment

a) Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more systemic therapies

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

The resolution is based on the patient numbers from the resolution of 7 March 2019 on Tisagenlecleucel for the therapeutic indication of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more systemic therapies.

Justification:

The calculation of the patient numbers presented in this procedure is largely methodologically and mathematically incomprehensible. Because of the multi-step estimation procedure with unclear data basis and possibly contradictory effects, the number of patients reported by the pharmaceutical manufacturer is subject to uncertainties. In the opinion of the G-BA, the patient numbers available here do not represent a clearly better estimate than the patient numbers from the resolution on Tisagenlecleucel from 7 March 2019 on the same therapeutic indication of relapsed or refractory DLBCL after more than two systemic pre-therapies; the latter will therefore continue to be used.

b) Adult patients with relapsed or refractory primary mediastinal large B-cell lymphoma (PMBCL) after two or more systemic therapies

In the dossier, the pharmaceutical manufacturer does not separately calculate the number of patients with relapsed or refractory PMBCL after two or more systemic therapies.

The following calculation is based on the calculation steps performed by the pharmaceutical manufacturer and evaluated by IQWiG in the dossier assessment. This calculation is subject to uncertainties because of the unclear data basis on the assumed proportions of conventionally treated patients and patients with failure of first- and second-line therapy. In addition, no patients with relapse or refractory disease after the third or later therapy line are considered.

Because no specific incidence rates for PMBCL are available for German patients, an incidence rate of 0.042 per 100,000 inhabitants in the US is assumed for PMBCL based on the publication of Liu et al. of 2016[4] and transferred to German patients. Based on the estimated number of 81,757,000 people living in Germany as of 31 December 2017, this results in 34 new cases of PMBCL in Germany in 2017.

The 2nd calculation step carried out by the pharmaceutical manufacturer (in which the target population is restricted to conventionally treated patients with PMBCL) is not applied. On one hand, the product information on YESCARTA® does not restrict the treatment to patients with conventional pre-therapies. On the other hand, patients who have previously been treated in clinical studies are still eligible for treatment with axicabtagene ciloleucel in the SHI system even after participation in the study.

The patient group is narrowed down to the target population using the following calculation steps (see IQWiG G-18-19 dossier assessment)[5]:

[4] Liu et al. Racial patterns of patients with primary mediastinal large B-cell lymphoma: SEER analysis. Medicine (Baltimore) 2016; 95(27): e4054

[5] IQWiG report – no. 716 Axicabtagene ciloleucel (primarily mediastinal large B-cell lymphoma) – G18-19, Version 1.0, 29 January 2019

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1. The review by Li et al.[6] states that approx. 60–70% of PMBCL patients are cured through first-line therapy. It is therefore assumed that first-line therapy fails in 30–40% of patients. This assumed value is subject to uncertainty because no deaths are considered. The source used also refers only to patients with DLBCL who have received first-line treatment with R-CHOP[7]. This calculation step results in a range of 10–14 PMBCL cases with failure of first-line therapy.
2. A value of 64% is assumed for the failure of the second-line therapy. In addition, an uncertainty margin of ± 10 is applied. This results in 6–10 cases of PMBCL with second-line therapy failure.
3. 88.9% of the German population is covered by SHI. This results in 5–9 patients in the target population.

Because of the uncertainties described, both over- and underestimation of patient numbers are possible.

6 Li et al. Diffuse cell B-cell lymphoma. Pathology (Phila) 2018; 50(1): 74–87.
7 Rituximab in combination with cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone

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2.3 Requirements for quality-assured application

A. Regulatory requirements for marketing authorisation

The requirements of the product information and the Risk Management Plan (RMP) under the terms of the marketing authorisation must be taken into account. The European Medicines Agency (EMA) provides the contents of the specialist information as well as the conditions or restrictions for the safe and effective use of Yescarta® (active ingredient: axicabtagene ciloleucel) agreed upon in the context of the market authorisation under the following link (last access: 6 March 2019):

https://www.ema.europa.eu/documents/product-information/yescarta-epar-product-information_de.pdf

According to the requirements of the European Medicines Agency (EMA) regarding additional measures to minimise risk, the pharmaceutical manufacturer must provide training material and a patient emergency card. The training material for all healthcare professionals who are to prescribe, deliver, and administer axicabtagene ciloleucel contains instructions for the identification, treatment, and monitoring of cytokine-release syndrome and neurological side effects. It also includes instructions on the thawing of cells, the availability of four doses of tocilizumab at the site of treatment, the provision of relevant information to patients, and the full and adequate reporting of adverse events.

The patient training programme is designed to educate patients about the risks of cytokine release syndrome and serious neurological side effects as well as the need to report symptoms immediately to the attending physician, stay near the treatment facility for at least four weeks after axicabtagene ciloleucel infusion, and carry their patient emergency card with them at all times.

B. Further requirements for the quality-assured use of axicabtagene ciloleucel in qualified treatment facilities

Against the background of the highly malignant and advanced disease of the patients considered here, the immunosuppressive measures necessary for the administration of axicabtagene ciloleucel as well as the possible very severe CAR-T cell-specific side effects such as CRS[8] and CRES[9], treatment with axicabtagene ciloleucel represents a highly specialised and complex medical service.

The medicinal product must be used at a qualified treatment facility in accordance with the instructions in the summary of product characteristics. Therapy should be started and supervised under the guidance and supervision of healthcare professionals with experience in the treatment of haematological malignancies who are trained in the use of axicabtagene ciloleucel and the management of patients treated with this medicinal product.

An optimal structure and process quality of the treatment facility is required for an optimal benefit-risk assessment for the respective patient and for guaranteeing patient safety by fast and appropriate care, among other things in the event of the occurrence of CAR-T cell-specific side effects such as CRS[8] and CRES[9]. The infrastructure of the treatment facility must also

[8] Cytokine-release syndrome
[9] CAR-T-related encephalopathy syndrome

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ensure adequate handling of the final cell product because incorrect handling can relevantly limit the viability of the CAR-T cells and thus the probability of therapeutic success.

Against this background, in order to ensure a reliable and quality-assured supply of the medicinal product, in particular from the point of view of ensuring sufficient patient safety, it is appropriate but also necessary to establish more detailed requirements for the quality-assured use of the medicinal product, in particular with regard to the adequate qualification of a treatment facility.

Taking into account the consistent recommendations of the expert organisations and persons of medical science and practice in the context of the benefit assessment, the Federal Joint Committee assumes that a quality-assured supply of the medicinal product axicabtagene ciloleucel can take place in accordance with the following requirements for quality-assured use. Axicabtagene ciloleucel may only be used at a qualified treatment facility, which must meet at least the following criteria.

1. Requirements for the qualification of the treatment facilities

1.1 Extensive experience in the treatment of the respective underlying malignant disease

1.1.1 Documented by the treatment of ≥ 50 cases of large cell B-cell lymphoma in adults (C83.3, C85.1 or C85.2 after ICD-10-GM-2018) within the last three years, and participating in studies of the German Lymphoma Alliance (GLA) or a comparable study group.

Grounds:

The establishment of a minimum quantity in the form of numbers of cases as evidence of sufficient experience to supply the medicinal product is appropriate and justified. The authority to determine minimum quantities is based on Section 35a paragraph 1, sentence 3, number 6 in conjunction with paragraph 3 SGB V. Accordingly, the G-BA should also specify requirements for quality-assured use with the medicinal products with the resolution on the benefit assessment. From the general authority, it can be concluded that from the outset, the legislator did not want to limit the scope of the G-BA to a final catalogue of measures for quality-assured administration. Because the determination of minimum quantities in Section 35a paragraph 1, sentence 3, number 6 in conjunction with paragraph 3 SGB V is not explicitly mentioned as a measure for quality-assured use of medicinal products, it cannot be concluded that it is not covered by the authority. This corresponds to the fact that, according to the case law of the BSG, suitable requirements for minimum quantities (e.g. in the form of minimum patient numbers) can generally also be considered as a quality assurance measure. There is no doubt that minimum quantities can in principle be an instrument of quality assurance (BSG, judgement of 29 November 2017 – B 6 KA 32/16 R, cited by juris, marginal 37 et seq.). Based on the fundamental suitability and social-law recognition of minimum quantities as an instrument of quality assurance, it cannot be concluded from the special regulations on minimum quantities laid down in SGB V as a prerequisite for the provision of certain services by hospitals that minimum quantities in all other areas would be completely excluded as an instrument of quality assurance (cf. BSG, judgement of 29 November 2017 – B 6 KA 32/16 R, cited by juris, marginal 37 et

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seq.). In the light of this consideration, the regulations in Section 35a paragraph 1, sentence 3, number 6 in conjunction with paragraph 3 SGB V give the G-BA a sufficiently wide scope for the definition of requirements for the quality-assured use of medicinal products, which also includes the determination of minimum quantities.

R/r DLBCL and r/r PMBCL are rare diseases, which affect fewer than 1000 patients yearly in Germany. The treatment of r/r DLBCL or r/r PMBCL is a highly specialised and complex service, which requires a special level of practice and experience. For a medically adequate indication, an individual assessment of the available therapy alternatives is necessary because of the lack of comparative study data. Sufficient therapeutic experience in the treatment of DLBCL or PMBCL is therefore essential in order to adequately assess the benefit-risk ratio for the use of axicabtagene ciloleucel in multiple pre-treated patients compared with other possible therapy alternatives. Study data for the relationship between treatment volume and mortality specifically for the indication r/r DLBCL or r/r PMBCL are not available. However, for the disease acute myeloid leukaemia (AML), which has a similar complexity with regard to its disease characteristics and the course of therapy, there was a correlation between the amount of treatment and mortality[10]. From these points of view, there is a reasonable probability that a minimum number of cases will lead to considerable quality advantages with respect to the highly specialised and complex medical services available here.

Treatment cases are documented in accordance with the regulations adopted by the G-BA in the field of quality assurance. The application of the regulations adopted by the G-BA in the field of quality assurance remains unaffected in accordance with Item 3 of the requirements for quality-assured administration.

1.2 Extensive experience in cell therapy

1.2.1 As documented by > 120 allogeneic first transplantations reported to the German Registry for Stem Cell Transplantation / European Bone Marrow Transplantation Registry (DRST/EBMTR) within the last three reviewed years.

Grounds:

The use of axicabtagene ciloleucel represents a highly complex treatment approach because of, among other things, the immunosuppressive measures required in most cases and the possible serious side effects. Because of the novelty of the therapy approach, a connection between treatment quantity and treatment quality for axicabtagene ciloleucel and CAR-T cells cannot currently be demonstrated in studies. Therefore, in the present case, the closest therapy concept of allogeneic stem cell transplantation, which has been established for the present indication and treatment situation, is used. As with CAR-T cells, allogeneic stem cell transplantation requires the administration of high-intensity conditioning chemotherapy, which strongly compromises the patient's immune system. Dealing with severely immunosuppressed patients, including early diagnosis and the treatment of serious infections, is therefore decisive for the rate of serious or fatal complications for both therapeutic approaches. In addition, CAR-T cells as well as allogeneic stem cell

[10] Giri et al. Impact of hospital volume on outcomes of patients undergoing chemotherapy for acute myeloid leukaemia: a matched cohort study. Blood 2015 125:3359–3360

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transplantation are based on the immunogenic properties of human cells that trigger an immune response. Thus, both therapy approaches can lead to severe immune-mediated complications, which affect multiple organs. In the worst-case scenario, these can lead to death. For the lowest possible mortality and morbidity resulting from acute therapy complications, the rapid and qualified early detection of complications and appropriate intervention are essential. In treatment facilities with sufficient experience in allogeneic stem cell transplantation, it is ensured that personal experience with such complications exists, that the interface to intensive care medicine is adequately defined, that workflows are standardised, and that haemato-oncological expertise also flows into the field of intensive care medicine. There is also the handling of long-term complications and the aftercare of patients. While chronic graft-versus-host-disease is a well-known long-term complication for allogeneic stem cell transplantation, possible long-term sequelae from treatment with axicabtagene ciloleucel are largely unexplained. Potential long-term complications listed by the European Medicines Agency include sustained immunodeficiency or B-cell depletion, secondary tumours, and autoimmune diseases. In treatment facilities with sufficient experience in allogeneic stem cell transplantation or with outpatient specialists cooperating with these treatment facilities, structured aftercare is generally implemented in order to identify long-term consequential damage. For allogeneic stem cell transplantation, study data provide evidence of a causal relationship between treatment volume and mortality as well as the success of therapy (freedom from leukaemia, absence of relapse)[11,12]. Because the common characteristics described between CAR-T cells and allogeneic stem cell transplantation largely determine the quality and risks of the medical service, considerable quality advantages can also be expected for the CAR-T cells through the defined minimum quantities for the performance or detection of allogeneic stem cell transplantation. The present minimum quantities, which were calculated over three years, allow for the compensation of random fluctuations from personnel or organisational aspects. They also prevent a treatment facility from reaching a short-term threshold resulting from a medically unjustified increase in quantities.

Documentation is provided by the reporting of >120 allogeneic first transplantations to the German Registry for Stem Cell Transplantation/European Bone Marrow Transplantation Registry (DRST/EBMTR) within the last three years evaluated. In this respect, it is a special regulation that finally defines the documentation requirements in relation to other regulations of the G-BA (cf Item 3 of the Requirements for Quality Assured Application).

1.3 Personnel and technical requirements

1.3.1 The medical director and deputy director responsible for treating adults with axicabtagene ciloleucel must be specialists in internal medicine, haematology, and oncology. The medically responsible management or its deputy must have at least two years' professional experience in a treatment centre in which allogeneic stem

[11] Giebel et al. The impact of centre experience on results of reduced intensity: allogeneic haematopoietic SCT for AML. An analysis from the Acute Leukaemia Working Party of the EBMT. Bone Marrow Transplant. 2013 Feb;48(2):238-42.

[12] Loberiza et al. Transplant center characteristics and clinical outcomes after haematopoietic stem cell transplantation: what do we know. Bone Marrow Transplantation volume 31, pages 417–421 (2003)

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cell transplantations are carried out in accordance with the criteria set out in Points 1.1 and 1.2 below. If the activity is conducted on a part-time basis, allogeneic stem cell transplantations performed on the ward may be allocated proportionately to full-time work.

1.3.2 Requirements for the qualifications of the nursing service

1.3.2.1 The management and their representation on the ward for the care of patients treated with axicabtagene ciloleucel are nurses with oncological specialisation or have worked full-time for at least 36 months in a ward with a haematological-oncological specialisation and have participated in the in-house training for the treatment of patients with axicabtagene ciloleucel. If the activity is conducted on a part-time basis, the corresponding working hours may be allocated proportionately to full-time work.

1.3.2.2 Each shift is led by nurses who have worked full-time for at least 12 months in a haematological-oncological ward, have experience in the intensive chemotherapy of leukaemia/lymphoma patients, and have participated in in-house training for the treatment of patients with axicabtagene ciloleucel. If the activity is conducted on a part-time basis, the corresponding working hours may be allocated proportionately to full-time work.

1.3.3 Sufficient training and documented experience of the medical staff involved (doctors, nurses) in the treatment with cytotoxic and immunosuppressive substances as well as cryopreserved cells must be demonstrated.

2. Infrastructure and organisational requirements

2.1 Establishment of a tumour board:

2.1.1 The indication for treatment with axicabtagene ciloleucel in adults must be presented at an interdisciplinary tumour conference in which at least physicians with the following qualifications participate:

- Internal medicine, haematology and oncology
- Radiation therapy
- Pathology
- Diagnostic radiology

2.1.2 The date, participants and outcome of discussions at the tumour conference must be documented in writing.

2.2 The responsible pharmacy must be integrated into the treatment facility by binding regulations for the timely fulfilment of statutory requirements.

2.3 The rooms for the treatment of patients with axicabtagene ciloleucel are located in the vicinity of the intensive care unit. The treatment facility must have the necessary equipment to perform at all times endoscopy, including bronchoscopy, invasive ventilation, and renal replacement therapy. Specific SOPs[13] deal with complications of CAR-T cell therapy, including the use and sufficient availability of tocilizumab on site at all times in accordance with the specialist information. There is also a binding and

[13] Standard Operating Procedure

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regulated definition of the rapid and unhindered admission of intensive care patients to the intensive care unit.

2.4 There are SOPs[13] for clinical, instrumental, and laboratory chemical monitoring for the early detection of CRS[14] and CRES[15] as well as for the procedure for transferring the patient to the intensive care unit (e.g. decision-making authority, persons involved).

2.5 Medical care in accordance with specialist standards (internal medicine, haematology, and oncology) must be available without interruption for the inpatient care of patients treated with axicabtagene ciloleucel; at least one on-call service must be provided outside working hours.

2.6 When transferring to the intensive care unit, it must be ensured that a visit is carried out daily by a specialist in internal medicine, haematology and oncology. This physician must also have personal experience in the treatment with CAR T cells. The treatment concept on the intensive care unit must be discussed with this physician.

2.7 In addition, the following specialist disciplines must be available at all times; the necessary examinations and treatments should be possible without the need for patient transport (in alphabetical order):

- Ophthalmology
- Gastroenterology (endoscopy of the gastrointestinal tract)
- Vascular surgery
- Otorhinolaryngology
- Cardiology
- Laboratory medicine
- Microbiology (availability within 24 hours is sufficient)
- Nephrology (dialysis)
- Neurosurgery
- Neurology (with proof of participation in the in-house training programme)
- Pneumology (bronchoscopy)
- Psychiatry
- Radiology (with CT and MRI)
- Thoracic surgery
- Urology

Outside working hours, at least one on-call standby service must be provided. On-call duty means that a specialist of the treatment facility with the corresponding qualification certificates is available to the patient at any time (24 hours a day, seven days a week) within a maximum of 30 minutes.

[14] Cytokine release syndrome
[15] CAR-T-related encephalopathy syndrome

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2.8 Accommodation in specific rooms for patients in Risk groups 2 or 3 according to the guidelines of the Robert Koch Institute[16] is generally not required. However, it must be ensured that such accommodation is possible at all times.

2.9 Outpatient after-care

2.9.1 Medical care in accordance with specialist standards (internal medicine, haematology, and oncology) must be available at all times for outpatient follow-up of patients treated with axicabtagene ciloleucel.

2.9.2 The spatial environment must enable the outpatient care of immunosuppressed patients.

2.9.3 The spatial environment must make it possible to examine and treat patients with contagious infections separately. A suitable infrastructure for infusion treatment and the transfusion of blood products must be available.

2.10 Further quality assurance measures

The treatment facility participates in inter-institutional quality assurance and knowledge-generating care measures (registries, quality circles, and analysis of quality indicators) offered nationally or internationally by professional organisations, the pharmaceutical industry, and regulatory authorities.

2.11 Documentation

The documentation is part of the conditions imposed by the European Medicines Agency on pharmaceutical companies. The treatment facility must maintain the personnel and structural requirements for the connection to the planned register modules for CAR-T cells in the German Register for Stem Cell Transplantation (DRST), in the Paediatric Register for Stem Cell Transplantation (PRST), or in the Register of the European Society for Blood and Marrow Transplantation (EBMT) as well as for timely documentation. The following in particular should be documented:

- Prior therapies
- Adverse drug effects
- Type and duration of response
- Follow-up therapies
- Overall survival

3. The findings according to Items 1 and 2 regulate minimum requirements for the quality-assured use of axicabtagene ciloleucel. The validity of other provisions of the G-BA remains unaffected provided that these do not conflict with the minimum requirements.

[16] Recommendation of the Commission for Hospital Hygiene and Infection Prevention at the Robert Koch Institute (RKI). Hygiene requirements for the medical care of immunosuppressed patients. Bundesgesundheitsblatt [Federal Health Gazette] 2010 53:357–388.

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2.4 Treatment costs

The treatment costs are based on the information in the product information as well as the pharmaceutical manufacturer's information on the selling price from Module 3 of the dossier. YESCARTA® is not listed in the Lauer-Taxe® (the official German price list for all pharmaceuticals) because axicabtagene ciloleucel is only given to qualified, inpatient treatment facilities. The active ingredient is therefore not subject to the pharmaceutical price regulation, and there are no discounts according to Section 130 or Section 130a SGB V. The calculation is based on the selling price of the pharmaceutical manufacturer. This differs from the information usually taken into account in Lauer-Taxe.

As specified in the summary of product characteristics, axicabtagene ciloleucel is administered as a single intravenous infusion.

Axicabtagene ciloleucel is an autologous T cell therapy genetically modified *ex vivo* with a retroviral vector encoding a chimeric antigen receptor (CAR) directed against CD19. Accordingly, the concentration of CAR-positive viable T cells may vary between patient specific batches. Each patient-specific single infusion bag contains a dispersion of anti-CD19 CAR T cells in approximately 68 ml for a target dose of 2×10^6 CAR positive viable T cells per kilogram body weight (range $1 \times 10^6 – 2 \times 10^6$ cells/kg) with a maximum of 2×10^8 anti-CD19 CAR T cells.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Patient population a) and patient population b)				
Medicinal product to be assessed				
Axicabtagene ciloleucel	Single dose	1	1	1

Usage:

For dosages depending on body weight or body surface, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis. 1.72 m, average body weight: 77 kg). From this, a body surface of 1.90 m² is calculated (calculation according to Du Bois 1916)[17].

[17] Statistisches Bundesamt [German Federal Office for statistics] Micro-census 2017: Fragen zur Gesundheit; Körpermaße der Bevölkerung 2017 [Questions about health; body measurements of the 2017 population] [on-line]. 2 August 2018 [Accessed: 11 September 2018]. URL: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile.

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Designation of the therapy	Dosage	Dosage/ patient/ treatment days	Consumption according to potency/ treatment day	Treatment days/ patient/ year	Annual average consumption according to potency
Patient population a) and patient population b)					
Medicinal product to be assessed					
Axicabtagene Ciloleucel	2×10^6 CAR-positive viable T cells/kg[18]	1.54×10^8 CAR-positive viable T cells	1 single infusion bag	1	1 single infusion bag

Costs:

Costs of the medicinal product:

Designation of the therapy	Package sizes	Costs (Selling price of the pU)[19]	Value added tax	Cost
Patient population a) and patient population b)				
Medicinal product to be assessed				
Axicabtagene ciloleucel	1 single infusion bag (2×10^6 CAR-positive viable T cells/kg)	€ 327,000	€ 62,130.00[20]	€ 389,130.00

Costs for additional SHI services required:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular costs for the necessary medical treatment or the prescription of other services when using the drug to be evaluated in accordance with the product information, the costs incurred for this must be taken into account as costs for additional SHI services required.

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 usual expenditure in the course of the treatment are not shown.

Axicabtagene ciloleucel is an autologous cell product produced from the patient's own T cells. Leukapheresis is therefore regularly necessary to obtain the cell material. Because leukapheresis is part of the manufacture of the medicinal product under Section 4 paragraph 14 AMG, no further costs are incurred in this respect for the medicinal product to be assessed.

According to the product information for axicabtagene ciloleucel, the administration of lymphocyte-depleting chemotherapy is recommended prior to the administration of CAR-T cells. For this purpose, a regiment of fludarabine (30 mg/m^2) and cyclophosphamide (500

[18] For patients over 100 kg, the maximum dose is 2×10^8 CAR-positive viable T cells.
[19] Manufacturer's information on the selling price from module 3 of the dossier.
[20] In accordance with the information provided by the pharmaceutical manufacturer, the drug YESCARTA® will be invoiced without sales tax as of 1 April 2019. However, at present, there is no legally binding information available from a tax authority on the exemption of YESCARTA® from value-added tax.

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mg/m²) shall be administered intravenously on the 5th, 4th, and 3rd day prior to infusion. For dosages depending on body weight or body surface, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis. 1.72 m, average body weight: 77 kg). From this, a body surface of 1.90 m² is calculated (calculation according to Du Bois 1916)[17].

Type of service	Cost per package	Cost after deduction of statutory discounts[21,22]	Cost per service	Treatment days per year	Cost per patient/year
Patient population a) and patient population b)					
Medicinal product to be assessed					
Axicabtagene ciloleucel					
Lymphocyte depletion					
Fludarabine (30 mg/m², i.v.)	€ 118.20 1 × 50 mg	€ 111.34 (€ 1.77, € 5.09)	€ 222.68	3	€ 668.04
Cyclophosphamide (500 mg/m², i.v.)	€ 29.76 1 × 1,000 mg	€ 26.95 (€ 1.77, € 1.04)	€ 26.95	3	€ 80.85

Pharmaceutical retail price (Lauer-Taxe®) as last revised: 15 April 2019

Other SHI services:

The special agreement contractual unit costs of retail pharmacist services [Hilfstaxe"] (contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy retail 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: arbitral award to determine the mg prices for parenteral preparations from finished medicinal products in oncology in the Hilfstaxe according to Section 129 paragraph 5c, sentences 2-5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy retail price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for production and is only an approximation of the treatment costs. This presentation does not take into account, for example, the discounts 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 Appendix 3 to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"].

21 Sales discount pursuant to section 130 SGB V
22 Sales discount according to Section 130a SGB V

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3. Bureaucratic costs

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

On 31 October 2018, the pharmaceutical manufacturer submitted a dossier on the benefit assessment of axicabtagene ciloleucel to the G-BA in due time and in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure.

The benefit assessment of the G-BA was published on 1 February 2019 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 22 February 2019.

The oral hearing was held on 11 March 2019.

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 IQWiG also participate in the meetings.

The evaluation of the written statements received and the oral hearing were discussed at the meeting of the subcommittee on 24 April 2019, and the proposed resolution was approved.

At its meeting on 2 May 2019, the plenary adopted a resolution to amend the Pharmaceuticals Directive.

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Chronological course of consultation

Meeting	Date	Subject of consultation
Subcommittee Medicinal products	12 February 2019	Knowledge of the benefit assessment of the G-BA
Working group Section 35a	6 March 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 March 2019	Conduct of the oral hearing
Working group Section 35a	19 March 2019 2 April 2019 16 April 2019	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by IQWiG, and the evaluation of the statement procedure
Subcommittee Medicinal products	24 April 2019	Concluding discussion of the proposed resolution
Plenary	2 May 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 2 May 2019

Federal Joint Committee
in accordance with Section 91 SGB V
Chair

Prof Hecken

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