Gemeinsamer Bundesausschuss

# Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Axicabtagene Ciloleucel (reassessment after the deadline: (diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma))

of 3 November 2022

**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.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to 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 assessment of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 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 and prove the additional benefit in comparison with 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). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the 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 to that effect 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 medicinal product 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 decides 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.

## 2. Key points of the resolution

The relevant date for axicabtagene ciloleucel in accordance with Chapter 5, Section 8, paragraph 1, number 5 of the Rules of Procedure of the G-BA (VerfO) is 15 May 2022. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 12 May 2022.

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

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation 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 company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 August 2022 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G22-19) 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 assessed the studies relevant for the marketing authorisation considering their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, 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.

## 2.1 Additional benefit of the medicinal product

### 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 diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

**Therapeutic indication of the resolution (resolution of 3 November 2022):**

see the approved therapeutic indication

### 2.1.2 Extent of the additional benefit and significance of the evidence

a) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy

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

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

b) Adults with relapsed or refractory primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy

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

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

By G-BA's resolution of 2 May 2019, a non-quantifiable additional benefit was identified for axicabtagene ciloleucel (Axi-Cel) in adults with DLBCL and PMBCL, after two or more lines of systemic therapy. The validity of the resolution was limited until 15 May 2022 with the condition that the pharmaceutical company submits the complete results of the 60-month data cut-off of the single-arm, pivotal, phase I/II KTE-C19-101 (ZUMA-1) study on all patient-relevant endpoints. Furthermore, the possibility of an indirect comparison with the 60-month

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

data cut-off of the ZUMA-1 study should be examined, as well as the possibility of using further evidence, for example from observational studies.

For the reassessment of the additional benefit of Axi-Cel, the pharmaceutical company submitted the results of the 60-month data cut-off of the ZUMA-1 study from 11 August 2021, the retrospective SCHOLAR-1 study, the European Society for Blood and Marrow Transplantation (EBMT) registry study KT-EU-471-0117 and a systematic literature review. Based on the results of the ZUMA-1 study and the SCHOLAR-1 study, an indirect comparison without bridge comparator was performed.

**ZUMA-1 study**

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

The ZUMA-1 study has been ongoing since April 2015 at a total of 24 study sites across North America (23) and Israel (1).

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

The study contains six cohorts. Cohort 1 included subjects with DLBCL and cohort 2 included subjects with TFL and PMBCL. Cohorts 3 to 6 are not considered for the benefit assessment due to the non-pivotal treatment.

In phase I, a total of 8 subjects with r/r DLBCL were enrolled to study adverse events (AEs) or dose-limiting toxicity for both lymphocyte depletion and Axi-Cel. In contrast to the first benefit assessment procedure, the pharmaceutical company does not present the phase I data in the dossier. For the present benefit assessment, therefore, the data from the previous benefit assessment procedure was used with regard to phase I.

In phase II, a total of 111 subjects were included, of which 81 subjects had DLBCL, 21 had TFL and 9 had PMBCL. This patient population is referred to as the FAS population in the ZUMA-1 study and corresponds to the ITT principle.

The period from the time of enrolment in the study, which corresponds to the time of leukapheresis, to infusion of Axi-Cel was 23 days.

Axi-Cel was administered as a single infusion. Concomitant medications allowed in case of cytokine release syndrome (CRS) or neurologic events were tocilizumab, corticosteroids and other immunosuppressants (CRS only). Post-treatment follow-up was planned between study

week 2 and study month 3, after which long-term follow-up was planned until month 24, followed by survival follow-up until the end of the study (maximum 15 years).

In relation to the FAS population, the median age of the patients was 58 years (DLBCL), 63 years (TFL) and 32 years (PMBCL). All subjects had an ECOG performance status of 0-1. Most subjects were in stage III or IV disease and did not show B-symptomatology at the time of enrolment in the study. > 70% of subjects with TFL, > 80% with DLBCL and > 50% with PMBCL had ≥ 2 risk factors based on the International Prognostic Index (IPI). There is no data on the lactate dehydrogenase (LDH) activity of the patients.

As part of the marketing authorisation procedure, the European regulatory authority used the results of the ZUMA-1 study in addition to the individual results of cohorts 1 and 2 to assess the benefit-risk ratio of Axi-Cel for subjects with both r/r DLBCL and r/r PMBCL.[2]. Taking into account the rarity of lymphoma PMBCL, the results of the ZUMA-1 study, which include all three lymphoma types, are therefore also taken into account in the present evaluation for the assessment of the extent of additional benefit for the patient population with r/r DLBCL as well as with r/r PMBCL.

**SCHOLAR-1 study**

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

The data from the MD Anderson Cancer Center (MDACC) study and the Specialised Program of Research Excellence (SPORE) study at the Mayo Clinic and University of Iowa (MC/IA) are observational studies. The MDACC study enrolled subjects with r/r DLBCL and TFL after two previous lines of therapy. The previous lines of therapy had to include rituximab-containing chemotherapy and platinum-containing salvage chemotherapy. The MC/IA study enrolled subjects with newly diagnosed lymphoma and prospectively documented their treatment or disease status.

In addition, the SCHOLAR-1 study contains data from the follow-up phase of two randomised, controlled phase III studies. The National Cancer Institute of Canada (NCIC) Cancer Trials Group (CTG) study LY.12 enrolled subjects with a relapse after anthracycline-containing chemotherapy. The study medication consisted of two different salvage chemotherapy regimens. The phase III CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study of the "French Lymphoma Academic Research Organization (LYSARC)" includes subjects with DLBCL that has primarily relapsed after anthracycline-containing chemotherapy. The study medication also consisted of two different salvage chemotherapy regimens in this study with the aim of subsequently performing a consolidating autologous stem cell transplant (SCT). After SCT, there was further randomisation to monitoring wait-and-see approach or maintenance treatment with rituximab.

**Indirect comparison between ZUMA-1 and SCHOLAR-1**

For the derivation of the additional benefit, the pharmaceutical company presents a historical indirect comparison without a bridge comparator between the ZUMA-1 and SCHOLAR-1 studies. Patient-individual data from the SCHOLAR-1 study was available to the pharmaceutical company.

The inclusion criteria for the historical comparison were determination of refractory disease status and receipt of subsequent therapy to treat 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 in the course of treatment when the subject was found to be refractory. Because fewer subjects have received subsequent therapy for treatment of the last refractory disease identified at this later time point, the analysis population in the "last refractory" set is smaller than in the "first refractory" set.

In contrast to the first benefit assessment procedure, the pharmaceutical company refers to the "last refractory" analysis population of the SCHOLAR-1 study (n = 861) and excludes persons with unknown ECOG-PS in the analysis for the indirect comparison (Survival FAS: N = 390). Analogous to the previous benefit assessment, the pharmaceutical company presents the patient characteristics as well as the overall survival for the analysis population with the exclusion of primary refractory subjects who are not covered by the therapeutic indication of Axi-Cel, as well as with the exclusion of subjects with an ECOG-PS >1 (n= 162) in the dossier. Uncertaintiesarise result from any selection effect due to the selection of the evaluable population of the SCHOLAR-1 study.

In the present benefit assessment procedure, there are further uncertainties compared to the initial assessment due to the changed healthcare context in the meantime compared to the SCHOLAR-1 study. In particular, the newer treatment options tafasitamab, polatuzumab vedotin and tisagenlecleucel are considered relevant by the scientific-medical societies in the current healthcare context, but were not the subject of the SCHOLAR-1 study.

Overall, when looking at patient characteristics, it appears that a larger percentage of subjects in the ZUMA-1 study have ≥ 3 risk factors according to IPI, a more advanced stage of disease, and a greater number of prior lines of therapy. A systematic assessment of potential confounders and effect modifiers was not submitted by the pharmaceutical company.

The indirect comparison presented refers exclusively to the endpoint of overall survival. Current data on other patient-relevant endpoints in the categories of morbidity, quality of life and safety are not available. With regard to the endpoint of overall survival, the pharmaceutical company presents different analyses: an analysis based on the 60-month data of the ZUMA-1 study using the Cox proportional hazards model in the dossier and propensity score matching (PSM)-based analyses in the technical report of 9 February 2018.

The PSM analyses for the endpoint of overall survival are only available for the data cut-off of the ZUMA-1 study from 11 August 2017 (12-month data). It is unclear why no evaluations are available at later points in time. Therefore, the PSM analyses are not used for the present benefit assessment. In addition, it must be taken into account that information regarding the identification and selection of confounders and effect modifiers is missing. 8 and 10 potential confounders or effect modifiers were considered in the PSM analyses. However, it is unclear how these have been identified.

In the analyses conducted using the Cox proportional hazards model, only two covariates were included: the type of refractoriness based on the "last refractory" analysis population and "any SCT at any time after refractory disease was identified".

Overall, it can thus be assumed for both methods that no systematic identification and selection of confounders and effect modifiers were carried out. Thus, it cannot be assumed that the study populations are sufficiently adjusted.

The effect estimators on overall survival for the indirect comparison between the ZUMA-1 and SCHOLAR-1 studies based on the Cox proportional hazards model presented in the dossier are at a hazard ratio of 0.33 (24-month data) and 0.37 (60-month data).

**EBMT registry study (KT-EU-471- 0117)**

Furthermore, the pharmaceutical company submits a status report (data cut-off of 7 December 2021) of the EBMT registry study KT-EU-471- 0117 commissioned within the scope of the marketing authorisation. This is a single-arm, multicentre, observational study to assess the safety profile of Axi-Cel in patients with relapsed or refractory DLBCL or PMBCL, after two or more lines of systemic therapy.

At the time of the data cut-off, 391 subjects were enrolled in the study, with data from 341 subjects available for the efficacy and safety analysis after 100 days. A total of 1,173 subjects were screened for enrolment in the registry study. Of these, 782 subjects were excluded from the evaluation due to missing data. The background for this large number of excluded patients and the concrete reasons for exclusion are unclear. A risk of bias due to a selection effect can therefore not be ruled out. During the oral hearing, medical experts acknowledged methodological problems with the data collection in the EBMT registry.

Due to the limitations of the EBMT registry study described above, it is not considered for the benefit assessment.

**On the systematic literature review**

The pharmaceutical company also submits observational data from everyday care in the form of a systematic literature review. The aim of the systematic literature review was to identify studies from the reality of care that allow statements to be made about the efficacy and safety of CAR-T cell therapies in r/r DLBCL, and to conduct a meta-analysis to quantify the efficacy and safety of these therapies.

Only subjects who were infused with Axi-Cel were considered. Untreated subjects were not included, e.g., due to deaths between leukapheresis and treatment, thus the ITT principle was not implemented. Furthermore, the criteria for recording response as well as survey standards for recording and assessing safety and AEs were not defined or documented in many of the included studies.

Due to the described limitations, the results of the systematic literature reviews are not considered for the benefit assessment.

**Extent of the additional benefit**

In summary, the additional benefit of Axi-Cel is assessed as follows:

Mortality

*Overall survival*

In relation to the FAS population, the median overall survival for the total population (subjects with DLBCL, TFL and PMBCL) was 17.4 months. The plateau of the Kaplan-Meier curves already observed at the 24-month data cut-off is confirmed by the update analysis after 60 months. The Kaplan-Meier (KM) estimator changes only slightly between month 24 (47.7%) and month 60 (40.5%). After 60 months, 60% of the patients had died.

Indirect comparison with the SCHOLAR-1 study showed a statistically significant advantage of Axi-Cel (hazard ratio = 0.37 [0.26; 0.52], $p < 0.0001$). The 60-month survival rate for patients in the ZUMA-1 study is 41% compared to 11% for patients in the SCHOLAR-1 study.

However, it should be noted that the data at month 60 of the ZUMA-1 study show different results for patients with DLBCL, TFL and PMBCL. The median overall survival in patients with DLBCL (15.7 months) is shorter than the overall survival in patients with TFL (64.1 months) and PMBCL (not assessable). The Kaplan-Meier estimator for overall survival decreased more in patients with DLBCL compared to month 24 than in patients with TFL, and remained constant in patients with PMBCL.

The ZUMA-1 study included a higher percentage of patients with PMBCL and TFL compared to the SCHOLAR-1 study (8% vs 1% and 21% vs 1%, respectively). For patients with PMBCL, no statements can be made based on the indirect comparison and the previous explanations due to the small number of patients.

It should be noted that part of the effect in the indirect comparison may be influenced by different effects towards DLBCL, TFL and PMBCL, leading to a bias in favour of Axi-Cel. Taking into account the explanations on the uncertainties with regard to the adjustment, the G-BA arrives at the assessment that the effect is not in a magnitude where it can be assumed with sufficient certainty that the differences are not solely due to systematic bias.

Morbidity

*Progression-free survival (PFS)*

Progression was assessed using the IWG criteria according to Cheson et al. from 2007[2]. The assessment was carried out by medical investigators as well as by central assessment.

For the present assessment, the results of the central assessment are used, taking into account the lower risk of bias. This does not preclude the use of assessments by medical investigators in other cases.

In this dossier, the results for the PFS endpoint are presented in relation to the FAS population and based on the data cut-off from 11 August 2018. An updated evaluation based on the 60-

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

month data cut-off is not available. The median PFS was submitted by the pharmaceutical company in summary for subjects with DLBCL and TFL and was 9.0 months for these sub-entities. For subjects with PMBCL, the median PFS had not been reached as of 11 August 2018.

Based on the total population of the ZUMA-1 study, the median PFS was 9.5 months. Kaplan-Meier estimators dropped to about 37% by month 18. By month 24, there is no change in the KM estimator, with the probability of patients being progression-free remaining at 37% at this point.

The endpoint PFS is a combined endpoint of mortality and partial response (PR) or complete response (CR). The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint overall survival. For the operationalisation of progression (in PR) according to the IWG criteria[2] of 2007, only morphological, imaging features of tumour extent or growth are considered. However, the symptoms perceived by patients are not taken into account. Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint of PFS.

Due to the single-arm study design, a comparative assessment of the study results on 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 response was assessed on the basis of the IWG criteria[2] of 2007. The achievement of CR is an important prognostic factor and relevant for the treatment decision. A CR associated with a noticeable reduction in disease symptoms for the patient is generally patient-relevant for the benefit assessment. The IWG criteria used[2] almost exclusively take into account morphological, imaging features of tumour extent or growth.

ORR assessed by medical investigators was the primary endpoint of the ZUMA-1 study. The results for the ORR endpoint are presented in this dossier in relation to the FAS population and based on the data cut-off from 11 August 2018. An updated evaluation based on the 60-month data cut-off is not available.

The response rate for subjects with DLBCL is 79%, for subjects with TFL 76% and for subjects with PMBCL 67%. For the total population, the response is 77%, with 55% of patients achieving a complete remission.

In addition, the ORR was also assessed through central assessment. The response for subjects with DLBCL and TFL was 67% and for subjects with PMBCL 78%. For the total population, the response was 68%, with 50% of patients achieving a complete remission.

Due to the single-arm study design, a comparative assessment of response or complete remission rate for both patient groups is not possible.

Quality of life

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

Side effects

Phase I of the ZUMA-1 study involved the collection of safety data including dose-limiting toxicity which was reviewed by an internal review team. Based on these data, the review team made recommendations for the further procedure in the ZUMA-1 study.

In phase II of the ZUMA-1 study, a fully comprehensive assessment of the adverse events (AE) was conducted up to study month 3 after infusion of Axi-Cel. For the period from study month 3 to study month 24 after infusion of Axi-Cel, only targeted AEs were recorded (neurologic events, haematological events, infections, autoimmune diseases and secondary malignancies).

The results on AEs refer to the safety population, which includes all subjects who received conditioning chemotherapy and any dose of Axi-Cel, and are based on the data cut-off from 11 August 2018. There was no systematic recording of AEs after month 24.

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

Severe AEs (CTCAE grade ≥ 3) with incidence ≥ 5% and > 1 event were most common in the SOC of blood and lymphatic system disorders. The PT encephalopathy in particular was shown to be a serious AE with an incidence ≥ 5% and > 1 event. In terms of AEs of special interest for identified risks with incidence ≥ 5% and > 1 event, neurologic events and various cytopenias were particularly evident for a CTCAE grade ≥ 3. A CRS with severity grade ≥ 3 according to the CRS Grading Scale according to Lee et al. was found in > 10% of subjects with DLBCL.

Due to the single-arm study design, a comparative assessment of the results on side effects for both patient groups is not possible.

Overall assessment/ conclusion

a) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy

For the assessment of the extent of additional benefit of axicabtagene ciloleucel (Axi-Cel) for the treatment of adults 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, the pharmaceutical company presented the results of the pivotal, single-arm, phase I/II ZUMA-1 study and an indirect historical comparison with the retrospective SCHOLAR-1 study for the endpoint of overall survival.

No current data was provided for the indirect comparison based on PSM analyses. Therefore, these evaluations are not used for the present benefit assessment. In the analyses using the Cox proportional hazards model, as in the PSM analyses, there are uncertainties regarding the identification of effect modifiers and confounders and thus a sufficient adjustment.

With regard to the single-arm study data, the plateau of the Kaplan-Meier curves already observed at the 24-month data cut-off could be confirmed with regard to overall survival by the update analysis of the ZUMA-1 study after 60 months. After 60 months, 40.5% of the patients were still alive. The 60-month data show differences in patients with DLBCL, TFL and PMBCL. There is a longer median overall survival in patients with TFL and PMBCL. Taking into account that the ZUMA-1 study included a higher percentage of patients with TFL and PMBCL than the SCHOLAR-1 study, a bias in favour of ZUMA-1 cannot be excluded. The effect is not of a magnitude where it can be assumed that the differences are not due to systematic bias alone.

Due to the single-arm study design of the ZUMA-1 study, no comparative assessment is possible for the endpoints on mortality, morbidity and side effects. Quality of life of patients was not recorded in the ZUMA-1 study.

In the overall assessment, a non-quantifiable additional benefit is identified since the scientific data basis does not allow quantification.

Significance of the evidence

For the benefit assessment, the data of the pivotal, single-arm ZUMA-1 study and an indirect historical comparison without a bridge comparator with the retrospective SCHOLAR-1 study on overall survival are available.

An adequate comparison based on the single-arm data is not possible. An indirect comparison without a bridge comparator is subject to significant uncertainties.

The reliability of data is assessed as a hint overall.

b) Adults with relapsed or refractory primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy

For the assessment of the extent of additional benefit of axicabtagene ciloleucel (Axi-Cel) for the treatment of adults 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, the pharmaceutical company presented the results of the pivotal, single-arm, phase

I/II ZUMA-1 study and an indirect historical comparison with the retrospective SCHOLAR-1 study for the endpoint of overall survival.

No current data was provided for the indirect comparison based on PSM analyses. Therefore, these evaluations are not used for the present benefit assessment. In the analyses using the Cox proportional hazards model, as in the PSM analyses, there are uncertainties regarding the identification of effect modifiers and confounders and thus a sufficient adjustment.

With regard to the single-arm study data, the plateau of the Kaplan-Meier curves already observed at the 24-month data cut-off could be confirmed with regard to overall survival by the update analysis of the ZUMA-1 study after 60 months. After 60 months, 40.5% of the patients were still alive. The 60-month data show differences between patients with DLBCL, TFL and PMBCL. No statements can be made for patients with PMBCL based on the indirect comparison due to the small number of patients.

Due to the single-arm study design of the ZUMA-1 study, no comparative assessment is possible for the endpoints on mortality, morbidity and side effects. Quality of life of patients was not recorded in the ZUMA-1 study.

In the overall assessment, a non-quantifiable additional benefit is identified since the scientific data basis does not allow quantification.

Significance of the evidence

The data from the pivotal, single-arm ZUMA-1 study are available for the benefit assessment. An adequate comparison based on the single-arm data is not possible.
The reliability of data is assessed as a hint overall.

### 2.1.3 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient axicabtagene ciloleucel (Axi-Cel) due to the expiry of the time limit of the resolution of 2 May 2019.

Axi-Cel has a marketing authorisation as an orphan drug. The present assessment refers to the indication "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". In the therapeutic indication considered, two patient groups were differentiated:

a) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy

The pharmaceutical company presents data from the single-arm, phase I/II ZUMA-1 study as well as further studies on Axi-Cel and historical controls. In addition, the results on mortality from the indirect historical comparison with the retrospective SCHOLAR-1 study are used.

With regard to the single-arm study data, the plateau of the Kaplan-Meier curves already observed at the 24-month data cut-off could be confirmed with regard to overall survival by the update analysis of the ZUMA-1 study after 60 months. TFL and PMBCL show a longer median survival time than DLBCL.

Taking into account the higher percentage of patients with TFL and PMBCL in the ZUMA-1 study compared to the SCHOLAR-1 study and uncertainties in the adjustment, the effect of the indirect comparison is not of a magnitude where it can be assumed that the differences are not due to systematic bias alone.

Due to the single-arm study design of the ZUMA-1 study, no comparative assessment is possible for the endpoints on mortality, morbidity and side effects. Quality of life was not recorded in the ZUMA-1 study.

In the overall assessment, a hint for a non-quantifiable additional benefit is identified since the scientific data basis does not allow quantification.

b) Adults with relapsed or refractory primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy

The pharmaceutical company presents data from the single-arm, phase I/II ZUMA-1 study as well as further studies on Axi-Cel and historical controls.

With regard to the single-arm study data, the plateau of the Kaplan-Meier curves already observed at the 24-month data cut-off could be confirmed with regard to overall survival by the update analysis of the ZUMA-1 study after 60 months. There are differences in the overall survival data for patients with DLBCL and PMBCL.

Taking into account the small number of patients, the indirect historical comparison with the retrospective SCHOLAR-1 study cannot be used for patients with PMBCL.

Due to the single-arm study design of the ZUMA-1 study, no comparative assessment is possible for the endpoints on mortality, morbidity and side effects. Quality of life was not recorded in the ZUMA-1 study.

In the overall assessment, a hint for a non-quantifiable additional benefit is identified since the scientific data basis does not allow quantification.

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

a) Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy

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

The resolution is based on the patient numbers from the resolution on the benefit assessment of tisagenlecleucel in the therapeutic indication of relapsed or refractory DLBCL, after two or more lines of systemic therapy of 17 September 2020.

Justification:

The calculation of the patient numbers presented in the present procedure is largely comprehensible and plausible, but overall fraught with uncertainties due to the multi-step estimation procedure with unclear data and possibly opposing effects.

In the opinion of the G-BA, the patient numbers available here do not represent a clearly better estimate compared to the patient numbers from the resolution on tisagenlecleucel of 17 September 2020, which is why the latter will continue to be used.

b) Adults with relapsed or refractory primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy

On the part of the pharmaceutical company, no separate calculation of patient numbers for subjects with relapsed or refractory PMBCL, after two or more lines of systemic therapy is performed in the dossier.
The following calculation is analogous to the resolution on the first benefit assessment of axicabtagene ciloleucel in the therapeutic indication of relapsed or refractory PMBCL, after two or more lines of systemic therapy of 2 May 2019. This calculation is based on the calculation steps carried out by the pharmaceutical company and assessed by IQWiG in the dossier assessment at that time and is subject to uncertainties due to an unclear data basis regarding the assumed percentages of subjects treated conventionally and those who failed first and second-line therapy. In addition, no subjects with relapse or refractoriness after the third or later line of therapy are considered.
Since no concrete incidence rates for PMBCL are available for German subjects, an incidence of 0.042 per 100,000 inhabitants in the USA is assumed for PMBCL based on the publication by Liu et al. from 2016[3] and transferred to German patients. Based on the estimated number of 84.1 million[4] people living in Germany on 30 June 2022, this results in 35 new PMBCL cases in Germany in 2022.

[3] Liu et al. Racial patterns of patients with primary mediastinal large B-cell lymphoma: SEER analysis. Medicine (Baltimore) 2016; 95(27): e4054.
[4] https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Bevoelkerung/Bevoelkerungsstand/Tabellen/liste-zensus-geschlecht-staatsangehoerigkeit.html#616584 [accessed 7 October 2022].

The 2nd calculation step, which is carried out by the pharmaceutical company and in which the target population is restricted to conventionally treated subjects with PMBCL was not applied. On the one hand, there is no restriction to subjects with conventional prior therapies in the product information for Yescarta, and on the other, subjects who were pretreated in clinical studies are still eligible for treatment with axicabtagene ciloleucel in the SHI system after participating in the study. The patient group is narrowed down to the target population using the following calculation steps (see IQWiG's dossier assessment G-18-19)[5]:

1. The review by Li et al. states that about 60% to 70% of PMBCL patients are cured by first-line therapy. Therefore, it is assumed that first-line therapy fails in 40% to 30% of subjects. This assumed percentage value is subject to uncertainties, as no deaths are taken into account and the source used only refers to patients with DLBCL who received first-line treatment with R-CHOP. This calculation step results in a range of 11 - 14 PMBCL cases with failure of first-line therapy.

2. A share of 64% is assumed for the failure of second-line therapy. In addition, an uncertainty margin of ± 10 is applied. This results in 6 - 10 PMBCL cases with second-line therapy failure.

3. 88.1% of the German population is insured under the SHI system. This results in 5 - 9 subjects in the target population.

Due to the uncertainties described, both an overestimation and an underestimation of patient numbers are possible.

### 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: 8 September 2022):

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

[5] IQWiG reports No. 716 Axicabtagene ciloleucel (primary mediastinal large B-cell lymphoma) - G18-19, version 1.0, 29.01.2019.

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 centre. For the infusion of axicabtagene ciloleucel in the present therapeutic indication, the quality assurance measures for the use of CAR-T cells in B-cell neoplasms apply (ATMP Quality Assurance Guideline, Annex 1).

## 2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 October 2022).

Axicabtagene ciloleucel is listed on LAUER-TAXE®, but is only dispensed to appropriate qualified inpatient treatment facilities. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 30 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic pack, in deviation from the LAUER-TAXE® data usually taken into account.

Axicabtagene ciloleucel is administered as a single intravenous infusion according to the information provided in the product information.

Axicabtagene ciloleucel concerns autologous T cells that have been genetically modified *ex vivo* with a retroviral vector encoding a chimeric antigen receptor (CAR) directed against CD19. Accordingly, the concentration of viable CAR-positive 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 x $10^6$ CAR-positive viable T cells per kilogram body weight (range 1 x $10^6$ - 2 x $10^6$ cells/kg) with a maximum of 2 x $10^8$ 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 |

Consumption:

For dosages depending on body weight or body surface, the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were applied (average body height: 1,72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Patient population a) and patient population b) | | | | | |
| Medicinal product to be assessed | | | | | |
| Axicabtagene ciloleucel | 2 x $10^6$ CAR-positive viable T cells/ kg | 1.54 x $10^8$ CAR-positive viable T cells | 1 single infusion bag | 1 | 1 single infusion bag |

Costs:

**Costs of the medicinal products:**

| Designation of the therapy | Packaging size | Costs (clinic purchase registry) | Costs of the medicinal product |
|---|---|---|---|
| Patient population a) and patient population b) | | | |
| Medicinal product to be assessed | | | |
| Axicabtagene ciloleucel | 1 single infusion bag | € 282,000.00 | € 282,000.00 |

LAUER-TAXE® last revised: 15 October 2022

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.

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

According to the product information of axicabtagene ciloleucel, the administration of lymphocyte-depleting chemotherapy is recommended prior to the administration of the CAR-T cells. For this, a regimen of fludarabine (30 mg/m$^2$) and cyclophosphamide (500 mg/m$^2$) should be administered intravenously on the 5th, 4th and 3rd day before 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 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)[6].

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I to the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in

[6] Statistisches Bundesamt (Federal Statistical Office). Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

| 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 | | | | | | | |
| Chemotherapy for lymphocyte depletion | | | | | | | |
| Cyclophosphamide<br>500 mg/m² = 950 mg<br>on day 5, 4 and 3 before the infusion | 6 x<br>500 mg | € 84.41 | € 1.77 | € 9.25 | € 73.39 | 3 | € 73.39 |
| Fludarabine<br>30 mg/m² = 57 mg<br>on day 5, 4 and 3 before the infusion | 1 x 50 mg | € 118.50 | € 1.77 | € 5.09 | € 111.64 | 3 | € 669.84 |

*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 € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost

representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

## 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

On 12 May 2022, the pharmaceutical company submitted a dossier for the benefit assessment of axicabtagene ciloleucel to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 5 VerfO.

The benefit assessment of the G-BA was published on 15 August 2022 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 5 September 2022.

The oral hearing was held on 26 September 2022.

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 were discussed at the session of the subcommittee on 25 October 2022, and the draft resolution was approved.

At its session on 3 November 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal products | 9 August 2022 | Information of the benefit assessment of the G-BA |
| Working group Section 35a | 20 September 2022 | Information on written statements received; preparation of the oral hearing |

| | | |
|---|---|---|
| Subcommittee Medicinal products | 26 September 2022 | Conduct of the oral hearing |
| Working group Section 35a | 4 October 2022<br>18 October 2022 | Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure |
| Subcommittee Medicinal products | 25 October 2022 | Concluding discussion of the draft resolution |
| Plenum | 3 November 2022 | Adoption of the resolution on the amendment of Annex XII AM-RL |

Berlin, 3 November 2022

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

Prof. Hecken