Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee 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

At its meeting on 2 May 2019, the Federal Joint Committee (G-BA) decided to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive) in the version dated 18 December 2008/22 January 2009 (BAnz. No. 49a of 31 March 2009), as last amended on TT. Monat JJJJ (BAnz AT TT.MM.JJJJ BX), as follows:

I. Annex XII is expanded to include the active ingredient axicabtagene ciloleucel in alphabetical order as follows:

axicabtagene ciloleucel

Resolution from: 2 May 2019
Entry into force on: 2 May 2019
BAnz AT TT. MM JJJJ Bx

Therapeutic indication (according to marketing authorisation dated 23 August 2018):

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. Extent of the additional benefit of the medicinal product

Axicabtagene ciloleucel has been approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan drugs. Pursuant to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medicinal benefit is considered to be already proven through the grant of marketing authorisation.

According to Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure, the Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups experiencing a therapeutically significant additional benefit. This quantification of the additional benefit is based on the criteria laid down in Chapter 5 Section 5 paragraph 7, numbers 1 to 4 of the Rules of Procedure.

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

Extent of additional benefit of axicabtagene ciloleucel:

Non-quantifiable

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

Extent of additional benefit of axicabtagene ciloleucel:

Non-quantifiable

Study results according to endpoints:[1]

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

- ZUMA-1 study: single-arm, multi-centre phase I/II study (24-month data cut-off: 11 August 2018)[2]
- Indirect historical comparison with SCHOLAR-1: international retrospective study consisting of data from two observational studies (MAYO and MDACC) and two randomised controlled phase III studies (CORAL and LY12).

Mortality

End-point	**ZUMA-1**									
	Phase I[a]		**Phase II**							
			DLBCL		**TFL**[3]		**PMBCL**		**Total**	
	N	Median survival time in months[b] [95% CI] *Patients with event n (%)*	N	Median survival time in months[b] [95% CI] *Patients with event n (%)*	N	Median survival time in months[b] [95% CI] *Patients with event n (%)*	N	Median survival time in months[b] [95% CI] *Patients with event n (%)*	N	Median survival time in months[b] [95% CI] *Patients with event n (%)*
Overall survival (OS)										
FAS population[c]										
	8	-[d] 5 *(63)*	81	15.7 [11.1; n.c.] *46 (57)*	21	n.a. [10.5; n.c.] *9 (43)*	9	n.a. [2.9; n.c.] *3 (33)*	111	17.4 [11.6; n.c.] *58 (52)*
OS to month	N	K-M estimator [95% CI]	N	K-M estimator [95% CI]	N	K-M estimator [95% CI]	N	K-M estimator [95% CI]	N	K-M estimator [95% CI]
6	8	-[d]	81	81.5 [71.2; 88.4]	21	76.2 [51.9; 89.3]	9	88.9 [43.3; 98.4]	111	81.1 [72.5; 87.2]
12	8	-[d]	81	56.8 [45.3; 66.7]	21	66.7 [42.5; 82.5]	9	66.7 [28.2; 87.8]	111	59.5 [49.7; 67.9]
18	8	-[d]	81	45.7 [34.6; 56.1]	21	57.1 [33.8; 74.9]	9	66.7 [28.2; 87.8]	111	49.5 [40.0; 58.4]
24	8	-[d]	81	43.2 [32.3; 53.6]	21	57.1 [33.8; 74.9]	9	66.7 [28.2; 87.8]	111	47.7 [38.2; 56.7]

1 Data from the amendment of the G-BA (published on 2 May 2019) unless otherwise stated.
2 Unless otherwise stated.
3 Transformed follicular lymphoma

Mortality: Indirect historical comparison with SCHOLAR-1

Endpoint	ZUMA-1		SCHOLAR-1		ZUMA-1 vs. SCHOLAR-1
	N	Median survival time in months	N	Median survival time in months	Standardised difference [95% CI]
Overall survival – FAS population[c)]					
	116	n.a.	390	4.3	n.a. [n.a.; 17.0]
OS rate to month	N	Survival rate	N	Survival rate	Standardised difference [95% CI]
6	116	0.73	390	0.39	1.87 [1.60; 2.21]
12	116	0.58	390	0.21	2.82 [2.22; 3.64]
18	116	0.52	390	0.16	3.19 [2.42; 4.27]
24	116	0.50	390	0.14	3.73 [2.78; 5.14]
	N	Number of patients included in the analysis n (%)	N	Number of patients included in the analysis n (%)	Hazard ratio[m)] [95% CI] p value
	116	112 (97)	390	340 (87)	0.30 [0.22; 0.41] < 0.0001

Morbidity

Endpoint	ZUMA-1					
	Cohort 1 (DLBCL)		**Cohort 2[e)] (TFL and PMBCL)**		**Total**	
	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*
Progression-free survival (PFS) – FAS population[c)]						
Evaluated by a central reviewer[f)]						
	81	7.3 [5.2; 14.6] *50 (62)*	30	n.a. [3.0; n.a.] *13 (43)*	111	9.5 [6.1; 15.4] *63 (57)*

(Continuation)

Endpoint	ZUMA-1					
	Cohort 1 (DLBCL)		Cohort 2[e] (TFL and PMBCL)		Total	
	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*	N	Median time in months [95% CI] *Patients with event n (%)*
PFS to month	N	K-M estimator [95% CI]	N	K-M estimator [95% CI]	N	K-M estimator [95% CI]
6	81	58.5 [46.8; 68.4]	30	66.5 [45.4; 81.0]	111	60.4 [50.4; 69.0]
12	81	42.9 [31.5; 53.7]	30	54.8 [34.2; 71.4]	111	45.9 [35.9; 55.2]
18	81	33.8 [23.2; 44.8]	30	50.9 [30.7; 67.9]	111	38.2 [28.6; 47.7]
24	81	33.8 [23.2; 44.8]	30	50.9 [30.7; 67.9]	111	38.2 [28.6; 47.7]

Endpoint	ZUMA-1							
	DLBCL		TFL		PMBCL		Total	
	N	Response rate in % [95% CI][g] *Patients with event n (%)*	N	Response rate in % [95% CI][g] *Patients with event n (%)*	N	Response rate in % [95% CI][g] *Patients with event n (%)*	N	Response rate in % [95% CI][g] *Patients with event n (%)*
Objective response rate (ORR) – FAS population[c]								
Evaluated by the investigator								
ORR	81	79 [69; 87] *64 (79)*	21	76 [53; 92] *16 (76)*	9	67 [30; 93] *6 (67)*	111	77 [69; 85] *86 (77)*
CR	81	- *41 (51)*	21	- *14 (67)*	9	- *6 (67)*	111	- *61 (55)*
PR	81	- *23 (28)*	21	- *2 (10)*	9	- *0 (0)*	111	- *25 (23)*

(Continuation)

Endpoint	ZUMA-1							
	DLBCL		TFL		PMBCL		Total	
	N	Response rate in % [95% CI][g)] *Patients with event n (%)*	N	Response rate in % [95% CI][g)] *Patients with event n (%)*	N	Response rate in % [95% CI][g)] *Patients with event n (%)*	N	Response rate in % [95% CI][g)] *Patients with event n (%)*
Evaluated by a central reviewer								
ORR	81	67 [55; 77] *54 (67)*	21	67 [43; 85] *14 (67)*	9	78 [40; 97] *7 (78)*	111	68 [58; 76] *75 (68)*
CR	81	- *39 (48)*	21	- *10 (48)*	9	- *6 (67)*	111	- *55 (50)*
PR	81	- *15 (19)*	21	- *4 (19)*	9	- *1 (11)*	111	- *20 (18)*

Health related quality of life

Was not collected

Side effects

Endpoint[h)]	Phase I[a)]		Phase II							
			DLBCL		TFL		PMBCL		Total	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
Adverse events (AE; total rates)										
AEs on the day of leukapheresis and the following day										
AE (total)	7	4 *(57)*	77	55 *(71)*	16	10 *(63)*	8	4 *(50)*	101	69 *(68)*
Severe AE (CTCAE Grade ≥ 3)	7	2 *(29)*	77	25 *(32)*	16	2 *(13)*	8	2 *(25)*	101	29 *(29)*
Serious AE (SAE)	7	0 *(0)*	77	*9 (12)*	16	*1 (6)*	8	2 *(25)*	101	12 *(12)*
AEs from the beginning of conditioning chemotherapy to infusion of Axi-Cel										
AE (total)	7	6 *(86)*	77	67 *(87)*	16	14 *(88)*	8	8 *(100)*	101	89 *(88)*
Severe AE (CTCAE Grade ≥ 3)	7	4 *(57)*	77	42 *(55)*	16	6 *(38)*	8	2 *(25)*	101	50 *(50)*
Serious AE (SAE)	7	0 *(0)*	77	9 *(12)*	16	0 *(0)*	8	0 *(0)*	101	9 *(9)*

Endpoint[h)]	Phase I[a)]		Phase II							
			DLBCL		TFL		PMBCL		Total	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
AEs from start of infusion of Axi-Cel until 3 months after infusion										
AE (total)	7	7 *(100)*	77	77 *(100)*	16	16 *(100)*	8	8 *(100)*	101	101 *(100)*
Severe AE (CTCAE Grade ≥ 3)	7	7 *(100)*	77	75 *(97)*	16	15 *(94)*	8	7 *(88)*	101	97 *(96)*
Serious AE (SAE)	7	3 *(43)*	77	33 *(43)*	16	9 *(56)*	8	3 *(38)*	101	45 *(45)*
Severe AE (CTCAE grade ≥ 3) with incidence ≥ 5% and > 1 event at the SOC level										
Blood and lymphatic system disorders										
	7	6 *(86)*	77	60 *(78)*	16	13 *(81)*	8	6 *(75)*	101	79 *(78)*
Cardiac disorders										
	7	-	77	7 *(9)*	16	3 *(19)*	8	-	101	10 *(10)*
Gastrointestinal disorders										
	7	2 *(29)*	77	7 *(9)*	16	3 *(19)*	8	-	101	10 *(10)*
General disorders and administration site conditions										
	7	3 *(43)*	77	14 *(18)*	16	4 *(25)*	8	-	101	19 (19)
Infections and infestations										
	7	4 *(57)*	77	20 *(26)*	16	5 *(31)*	8	-	101	26 *(26)*
Investigations										
	7	4 *(57)*	77	36 *(47)*	16	5 *(31)*	8	3 *(38)*	101	44 *(44)*
Metabolism and nutrition disorders										
	7	5 *(71)*	77	30 *(39)*	16	7 *(44)*	8	-	101	38 *(38)*
Benign, malignant, and non-specific neoplasms (including cysts and polyps)										
	7	-	77	6 *(8)*	16	-	8	-	101	7 *(7)*
Nervous system disorders										
	7	4 *(57)*	77	20 *(26)*	16	7 *(44)*	8	2 *(25)*	101	29 *(29)*
Psychiatric disorders										
	7	-	77	10 *(13)*	16	3 *(19)*	8	-	101	14 *(14)*
Renal and urinary disorders										
	7	-	77	5 *(6)*	16	2 *(13)*	8	-	101	7 *(7)*
Respiratory, thoracic and mediastinal disorders										
	7	4 *(57)*	77	13 *(17)*	16	-	8	2 *(25)*	101	16 *(16)*

Endpoint[h)]	Phase I[a)]		Phase II							
			DLBCL		TFL		PMBCL		Total	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
Vascular disorders										
	7	-	77	14 *(18)*	16	4 *(25)*	8	-	101	19 *(19)*
Serious AE (SAE) with incidence ≥ 5% and > 1 event at the PT level										
Encephalopathy										
	7	-	77	16 *(21)*	16	2 *(13)*	8	-	101	19 *(19)*
Pyrexia										
	7	-	77	7 *(9)*	16	-	8	-	101	8 *(8)*
Confused state										
	7	-	77	-	16	-	8	-	101	5 *(5)*
Febrile neutropenia										
	7	-	77	5 *(6)*	16	-	8	-	101	5 *(5)*
Lung infection										
	7	2 *(29)*	77	5 *(6)*	16	-	8	-	101	6 *(6)*
Pneumonia										
	7	-	77	4 *(5)*	16	-	8	-	101	6 *(6)*
Agitation										
	7	-	77	-	16	2 *(13)*	8	-	101	-
Cardiac arrest										
	7	-	77	-	16	2 *(13)*	8	-	101	-
AE of special interest for identified risks with incidence ≥ 5% and > 1 event										
Cytokine-release syndrome (CRS)										
Any degree of severity	7	6 *(86)*	77	73 *(95)*	16	13 *(81)*	8	8 *(100)*	101	94 *(93)*
Severity ≥ 3[i)]	7	-	77	10 *(13)*	16	-	8	-	101	11 *(11)*
Neurological events										
Any degree of severity	7	6 *(86)*	77	50 *(65)*	16	12 *(75)*	8	4 *(50)*	101	66 *(65)*
CTCAE grade ≥ 3	7	4 *(57)*	77	22 *(29)*	16	6 *(38)*	8	3 *(38)*	101	31 *(31)*

Endpoint[h)]	Phase I[a)]		Phase II							
			DLBCL		TFL		PMBCL		Total	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
Thrombocytopenia[j)]										
Any degree of severity	7	4 *(57)*	77	51 *(66)*	16	8 *(50)*	8	4 *(50)*	101	63 *(62)*
CTCAE grade ≥ 3	7	4 *(57)*	77	33 *(43)*	16	5 *(31)*	8	-	101	39 *(39)*
Persistent thrombocytopenia[k)]										
Any degree of severity	7	3 *(43)*	77	30 *(39)*	16	3 *(19)*	8	-	101	33 *(33)*
CTCAE grade ≥ 3	7	2 *(29)*	77	15 *(19)*	16	3 *(19)*	8	-	101	18 *(18)*
Neutropenia[l)]										
Any degree of severity	7	6 *(86)*	77	68 *(88)*	16	13 *(81)*	8	6 *(75)*	101	87 *(86)*
CTCAE grade ≥ 3	7	6 *(86)*	77	64 *(83)*	16	10 *(63)*	8	6 *(75)*	101	80 *(79)*
Persistent neutropenia[k)]										
Any degree of severity	7	-	77	21 *(27)*	16	2 *(13)*	8	-	101	23 *(23)*
CTCAE grade ≥ 3	7	-	77	12 *(16)*	16	2 *(13)*	8	-	101	14 *(14)*
Anaemia										
Any degree of severity	7	4 *(57)*	77	56 *(73)*	16	10 *(63)*	8	3 *(38)*	101	69 *(68)*
CTCAE grade ≥ 3	7	4 *(57)*	77	36 *(47)*	16	7 *(44)*	8	2 *(25)*	101	45 *(45)*
Persistent anaemia[k)]										
Any degree of severity	7	-	77	20 *(26)*	16	-	8	-	101	21 *(21)*
CTCAE grade ≥ 3	7	-	77	-	16	-	8	-	101	-
Infections										
Any degree of severity	7	4 *(57)*	77	31 *(40)*	16	6 *(38)*	8	4 *(50)*	101	41 *(41)*
CTCAE grade ≥ 3	7	4 *(57)*	77	20 *(26)*	16	5 *(31)*	8	-	101	26 *(26)*

a) In Phase I, only patients with DLBCL were included.
b) In patients who have not died, the survival time is censored at the last known time.
c) The FAS population includes all study participants. Study participants were considered included when they signed the consent form and started leukapheresis.
d) For Phase I, deaths were recorded for reasons of safety. The overall survival analysis was not a Phase I objective; K-M estimators were therefore not reported.
e) A separate evaluation for patients with TFL and PMBCL is not available.
f) Information from the addendum to the study report of the ZUMA-1 study on the data cut-off of 11 August 2018. Patients who received a stem cell transplant before the documented progression were censored for assessment by the central reviewer.
g) Method according to Clopper-Pearson
h) The AE data was collected in accordance with MedDRA version 21.0 (Data cut-off 11 August 2018). The classification of the severity of AE was made according to CTCAE Version 4.03. AE refer to therapy-related AE defined as all AE that occurred after initiation of lymphocyte-depleting chemotherapy. A complete coverage of the AE was achieved until Month 3 after infusion; after this, only selected AE coverage was achieved until Month 24. These included: neurological events, haematological events, infections, autoimmune diseases, and secondary malignancies.
i) In accordance with CRS Grading Scale according to Lee et al., 2014.
j) Thrombocytopenia was identified by SMQ haematopoietic thrombocytopenia.
k) Persistent cytopenia was defined as the longest consecutive period of cytopenia of ≥ 30 days.
l) Neutropenia includes the PTs febrile neutropenia, neutropenia, and reduced neutrophil number.
m) Stratified Cox proportional hazards model with covariate therapy refractoriness and stem cell transplantation.

Abbreviations used:
AD = absolute difference; CR = complete remission; CRS= cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; DLBCL = diffuse large B-cell lymphoma; HR = Hazard Ratio; n.s. = not specified; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PR = partial remission; PT = Preferred Term; SMQ = Standardised MedDRA Query; SOC = System Organ Class; SAE = serious adverse event; TFL = transformed follicular lymphoma; AE = adverse event; vs. = versus

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

Approx. 440–700 patients

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

Approx. 5–9 patients

3. Requirements for quality-assured application

A. Regulatory requirements for marketing authorisation

The requirements of the product information and the Risk Management Plans (RMP) under the terms of the marketing authorisation must be taken into account. The European Medicines Agency (EMA) provides the contents of the product 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 program 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

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.

1.2 Extensive experience in cell therapy

1.2.1 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.

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 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 can be credited pro rata in relation 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 results of the consultation 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 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

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

2.4 There are SOPs[4] for clinical, instrumental, and laboratory chemical monitoring for the early detection of CRS[5] and CRES[6] 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 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.

[4] Standard Operating Procedure
[5] Cytokine release syndrome
[6] CAR-T-related encephalopathy syndrome

2.8 Accommodation in specific rooms for patients in Risk groups 2 or 3 according to the guidelines of the Robert Koch Institute[7] is generally not required. However, it must be ensured that such accommodation is possible at all times.

2.9 Outpatient aftercare

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.

[7] 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.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual therapy costs/patient
Axicabtagene ciloleucel[8,9,10]	€ 389,130.00[11]
Additional SHI services required	
Lymphocyte depletion	€ 748.89

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 April 2019

Other services covered by SHI funds:

Designation of the therapy	Type of service	Cost per unit	Number per cycle	Number per patient per year	Cost per patient per year
Lymphocyte depletion					
Fludarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	3	€ 243
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	3	€ 243

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

Designation of the therapy	Annual treatment costs/patient
Axicabtagene ciloleucel[8,9,10]	€ 389,130.00[11]
Additional SHI services required	
Lymphocyte depletion	€ 748.89

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 April 2019

8 Manufacturer's information on the selling price from module 3 of the dossier.
9 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.
10 This relates exclusively to the cost of the medicinal product YESCARTA®.
11 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.

Other services covered by SHI funds:

Designation of the therapy	Type of service	Cost per unit	Number per cycle	Number per patient per year	Cost per patient per year
Lymphocyte depletion					
Fludarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	3	€ 243
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	3	3	€ 243

II. Entry into force

1st The resolution will enter into force on the day of its publication on the Internet on the websites of the G-BA on 2 May 2019.

2nd The period of validity of the resolution is limited to 15 May 2022.

The justification for this resolution will be published on the website of the G-BA at www.g-ba.de .

Berlin, 2 May 2019

Federal Joint Committee
in accordance with Section 91 SGB V
Chair

Prof. Hecken