Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At its session on 3 November 2022, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII is amended as follows:

1. **The information on Axicabtagene Ciloleucel in the version of the resolution of 2 May 2019 (Federal Gazette AT 23.05.2019 B6) is repealed.**

2. **Annex XII shall be amended in alphabetical order to include the active ingredient Axicabtagene Ciloleucel as follows:**

Axicabtagene Ciloleucel

Resolution of: 3 November 2022
Entry into force on: 3 November 2022
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 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.

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

See new therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Axicabtagene ciloleucel 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 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

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

   Extent of the additional benefit and significance of the evidence of axicabtagene ciloleucel:

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

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

   Extent of the additional benefit and significance of the evidence of axicabtagene ciloleucel:

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

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.c.	The data are not assessable.
Morbidity	n.c.	The data are not assessable.
Health-related quality of life	∅	No data available.
Side effects	n.c.	The data are not assessable.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.c.: not calculable		

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.c.	The data are not assessable.
Morbidity	n.c.	The data are not assessable.
Health-related quality of life	∅	No data available.
Side effects	n.c.	The data are not assessable.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.c.: not calculable		

[1] Data from the dossier assessment of the G-BA (published on 15. August 2022), unless otherwise indicated.

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

and

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

ZUMA-1 study: single-arm, multicentre, phase I/II study (60-month data cut-off: 11.08.2021)[2]

Mortality

Endpoint	ZUMA-1									
	Phase I[a] (DLBCL)		Phase II							
			DLBCL		TFL[3]		PMBCL		Total	
	N	Median survival time in months[b] [95% CI] *Subjects with event n (%)*	N	Median survival time in months[b] [95% CI] *Subjects with event n (%)*	N	Median survival time in months[b] [95% CI] *Subjects with event n (%)*	N	Median survival time in months[b] [95% CI] *Subjects with event n (%)*	N	Median survival time in months[b] [95% CI] *Subjects with event n (%)*
Overall survival (OS)										
FAS population[c]										
	8	-[d] 5 (63)	81	15.7 [11.1; 36.2] 53 (65)	21	64.1 [10.5; n.a.] 11 (52)	9	n.a. [2.9; n.a.] 3 (33)	111	17.4 [11.6; 49.5] 67 (60)
OS in month	N	Kaplan-Meier estimator [95% CI]	N	Kaplan-Meier estimator [95% CI]	N	Kaplan-Meier estimator [95% CI]	N	Kaplan-Meier estimator [95% CI]	N	Kaplan-Meier estimator [95% CI]
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]
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]
60	8	-[d]	81	34.6 [24.5; 44.9]	21	52.4 [29.7; 70.9]	9	66.7 [28.2; 87.8]	111	40.5 [31.4, 49.5]

[2] Unless otherwise stated.
[3] Transformed follicular lymphoma

Mortality: Indirect historical comparison with SCHOLAR-1

(only for patient group a)

Endpoint	**ZUMA-1[e)]**		**SCHOLAR-1[f) g)]**		**ZUMA-1 vs SCHOLAR-1**
	N	Median survival time in months	N	Median survival time in months	Standardised difference [95% CI]
Median overall survival, in months					
	108	16.7	162	4.3	12.4 [6.4; 40.6]
OS rate in month	N	Survival rate	N	Survival rate	Standardised ratio [95% CI]
3	108	0.89	162	0.65	1.36 [1.21; 1.53]
6	108	0.77	162	0.38	2.02 [1.67; 2.56]
12	108	0.58	162	0.18	3.15 [2.32; 4.76]
18	108	0.50	162	0.17	2.95 [2.12; 4.64]
24	108	0.48	162	0.12	4.06 [2.69; 6.87]
36	108	0.44	162	0.12	3.70 [2.42; 6.34]
48	108	0.41	162	0.11	3.59 [2.33; 6.32]
60	108	0.41	162	0.11	3.59 [2.33; 6.32]
	N	Number of subjects included in the analysis n (%)	N	Number of subjects included in the analysis n (%)	Hazard ratio[h)] [95% CI] p value
	108	104 (96)	162	133 (82)	0.37 [0.26; 0.52] <0.0001

Morbidity

Endpoint	ZUMA-1					
	PMBCL		DLBCL and TFL		Total	
	N	Median survival time in months [95% CI] *Subjects with event n (%)*	N	Median survival time in months [95% CI] *Subjects with event n (%)*	N	Median survival time in months [95% CI] *Subjects with event n (%)*
Progression-free survival (PFS)[i] – FAS population						
Evaluated by central assessment						
	9	Not achieved [2.6; NE] 3 1	102	9.0 [6.1; 13.7] 40 23	111	9.5 [6.2; 14.6] 43 24
Disease progression Death (due to illness/ treatment)						
PFS in month	**N**	**Kaplan-Meier estimator [95% CI]**	**N**	**Kaplan-Meier estimator [95% CI]**	**N**	**Kaplan-Meier estimator [95% CI]**
6	9	66.7 [28.2; 87.8]	102	60.7 [50.3; 69.5]	111	61.2 [51.3; 69.6]
12	9	55.6 [20.4; 80.5]	102	43.8 [33.8; 53.3]	111	44.8 [35.1; 53.9]
18	9	55.6 [20.4; 80.5]	102	35.1 [25.7; 44.7]	111	36.8 [27.6; 46.0]
24	9	55.6 [20.4; 80.5]	102	35.1 [25.7; 44.7]	111	36.8 [27.6; 46.0]

Endpoint	ZUMA-1							
	DLBCL		TFL		PMBCL		Total	
	N	*Subjects with event n (%)*	N	*Subjects with event n (%)*	N	*Subjects with event n (%)*	N	*Subjects with event n (%)*
Objective response rate (ORR)[j] – FAS population[k]								
ORR assessed by the medical investigators								
OR (CR + PR), n (%)	81	64 (79)	21	16 (76)	9	6 (67)	111	86 (77)
CR, n (%)	81	41 (51)	21	14 (67)	9	6 (67)	111	61 (55)
PR, n (%)	81	23 (28)	21	2 (10)	9	0 (0)	111	25 (23)
ORR, in % [95% CI][l]	81	79 [69; 87]	21	76 [53; 92]	9	67 [30; 93]	111	77 [69; 85]

ORR evaluated by central assessment								
OR (CR + PR), n (%)	81	54 (67)	21	14 (67)	9	7 (78)	111	75 (68)
CR, n (%)	81	39 (48)	21	10 (48)	9	6 (67)	111	55 (50)
PR, n (%)	81	15 (19)	21	4 (19)	9	1 (11)	111	20 (18)
ORR, in % [95% CI] [l)]	81	67 [55; 77]	21	67 [43; 85]	9	78 [40; 97]	111	68 [58; 76]

Health-related quality of life

Was not recorded in the ZUMA-1 study.

Side effects

Endpoint [m)]	**ZUMA-1**									
	Phase I [a)] **(DLBCL)**		**Phase II**							
			DLBCL		**TFL**		**PMBCL**		**Total**	
	N	*Subjects with event n (%)*	N	*Subjects with event n (%)*	N	*Subjects with event n (%)*	N	*Subjects with event n (%)*	N	*Subjects with event n (%)*
Adverse events (AEs; overall rates)										
AEs on the day of leukapheresis and one day afterwards										
AEs (total)	7	4 (57)	77	55 (71)	16	10 (63)	8	4 (50)	101	69 (68)
Severe AEs CTCAE grade ≥ 3	7	2 (29)	77	25 (32)	16	2 (13)	8	2 (25)	101	29 (29)
SAE	7	0 (0)	77	9 (12)	16	1 (6)	8	2 (25)	101	12 (12)
AEs from the start of conditioning chemotherapy until the infusion of axicabtagene ciloleucel										
AEs (total)	7	6 (86)	77	67 (87)	16	14 (88)	8	8 (100)	101	89 (88)
Severe AEs CTCAE grade ≥ 3	7	4 (57)	77	42 (55)	16	6 (38)	8	2 (25)	101	50 (50)
SAE	7	0 (0)	77	9 (12)	16	0 (0)	8	0 (0)	101	9 (9)

Serious AEs (SAEs) with incidence ≥ 5% and > 1 event at 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)
B-cell lymphoma										
	7	-	77	4 (5)	16	-	8	-	101	-
Lung infection										
	7	2 (29)	77	5 (6)	16	-	8	-	101	6 (6)
Pneumonia										
	7	-	77	4 (5)	16	-	8	-	101	-
Agitation										
	7	-	77		16	2 (13)	8	-	101	-
Cardiac arrest										
	7	-	77	-	16	2 (13)	8	-	101	-
AEs 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)
Degree of severity ≥ 3[n)]	7	n. d.	77	10 (13)	16	1 (6)	8	0	101	11 (11)
Neurologic events										
Any degree of severity	7	6 (86)	77	50 (65)	16	12 (75)	8	4 (50)	101	66 (65)
Degree of severity ≥ 3	7	4 (57)	77	22 (29)	16	6 (38)	8	3 (38)	101	31 (31)
Thrombocytopenia[o)]										
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[p)]										
Any degree of severity	7	3 (43)	77	73 (95)	16	13 (81)	8	8 (100)	101	94 (93)
Degree of severity ≥ 3	7	n.d.	77	10 (13)	16	1 (6)	8	0	101	11 (11)
Neutropenia[q)]										
Any degree of severity	7	6 (86)	77	68 (88)	16	13 (81)	8	6 (75)	101	87 (86)
Degree of severity ≥ 3	7	6 (86)	77	64 (83)	16	10 (63)	8	6 (75)	101	80 (79)
Persistent neutropenia[p)]										
Any degree of severity	7	1 (14)	77	21 (27)	16	2 (13)	8	1 (13)	101	23 (23)
Degree of severity ≥ 3	7	1 (14)	77	12 (16)	16	2 (13)	8	0	101	14 (14)
Anaemia										
Any degree of severity	7	4 (57)	77	56 (73)	16	10 (63)	8	3 (38)	101	69 (68)
Degree of severity ≥ 3	7	4 (57)	77	36 (47)	16	7 (44)	8	2 (25)	101	45 (45)
Persistent anaemia										
Any degree of severity	7	1 (14)	77	26 (34)	16	2 (13)	8	1 (13)	101	29 (29)
Degree of severity ≥ 3	7	0	77	9 (12)	16	0	8	1 (13)	101	10 (10)
Infections										
Any degree of severity	7	4 (57)	77	31 (40)	16	6 (38)	8	4 (50)	101	41 (41)
Degree of severity ≥ 3	7	4 (57)	77	20 (26)	16	5 (31	8	n.d.	101	26 (26)
Bacterial infections										
Any degree of severity	7	1 (14)	77	14 (18)	16	1 (6)	8	0 (0)	101	15 (15)
Degree of severity ≥ 3	7	1 (14)	77	8 (10)	16	1 (6)	8	0 (0)	101	9 (9)
Viral infections										
Any degree of severity	7	4 (57)	77	15 (19)	16	2 (13)	8	2 (2)	101	19 (19)
Degree of severity ≥ 3	7	2 (29)	77	5 (6)	16	0 (0)	8	0 (0)	101	5 (5)
Opportunistic infections										
Any degree of severity	7	1 (14)	77	3 (4)	16	2 (13)	8	0 (0)	101	5 (5)

Degree of severity ≥ 3	7	0 (0)	77	0 (0)	16	0 (0)	8	0 (0)	101	0 (0)
Other infections										
Any degree of severity	7	3 (43)	77	22 (29)	16	5 (31)	8	3 (38)	101	30 (30)
Degree of severity ≥ 3	7	3 (43)	77	15 (19)	16	4 (25)	8	1 (13)	101	20 (20)

a) In phase I, only subjects with DLBCL were included.
b) For subjects who are not deceased, the survival time at the last known time is censored.
c) The FAS population comprises all included study participants. Study participants were considered included when they had signed the consent form and started leukapheresis.
d) For phase I, deaths were recorded in the context of safety. Analysis of overall survival was not a phase I objective, so Kaplan-Meier estimators were not reported.
e) For the indirect comparison, only subjects in cohorts 1 and 2 were considered in the dossier submitted by the pharmaceutical company for the ZUMA-1 study. The subjects in phase I were not considered; in the initial procedure for axicabtagene ciloleucel, these subjects were still considered.
f) Standardised survival rates were calculated for the SCHOLAR-1 study (details on the calculation of survival rates were presented in Supplement 1 of the SAP).
g) The analysis population of the SCHOLAR-1 study contains almost exclusively subjects with DLBCL. Only one subject each with TFL and PMBCL is included in the analysis population.
h) Stratified Cox proportional hazards model with covariates treatment refractoriness and stem cell transplant
i) Data on progression-free survival from the pharmaceutical company's dossier, based on the second update analysis (data cut-off of 11 August 2018).
j) Results on the objective response rate at the time of the second update analysis (data cut-off of 11 August 2018).
k) The sample size refers to the FAS, which comprises all included subjects. A subject was considered included when they signed the consent form and started leukapheresis.
l) The 95% CI was estimated using the Clopper-Pearson method.
m) The AEs were collected according to MedDRA version 21.0 (data cut-off of 11 August 2018). The classification of AE severity was done according to the CTCAE version 4.03. AEs refer to therapy-related AEs defined as all AEs that occurred after the start of lymphocyte-depleting chemotherapy. A complete recording of the AEs took place until month 3 after infusion, after which only selected AEs were recorded until month 24. These included: neurologic events, haematological events, infections, autoimmune diseases and secondary malignancies.
n) According to the CRS Grading Scale by Lee et al.,2014.
o) Thrombocytopenia was identified using the SMQ haematopoietic thrombocytopenia.
p) Persistent cytopenias were defined as the longest consecutive period of cytopenia of ≥ 30 days.
q) Neutropenia includes the PTs febrile neutropenia, neutropenia and decreased neutrophil count.

Abbreviations used:

CR = complete remission; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; DLBCL = diffuse large B-cell lymphoma; HR = hazard ratio; n.d. = no data; CI = confidence interval; N = number of persons evaluated; n.c. = not calculable; n.a. = not achieved; OR = objective response; ORR = objective response rate; PR = partial remission; PT = preferred term; SOC = system organ class; SAE = serious adverse event; TFL = transformed follicular lymphoma; AE= adverse event; vs = versus

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

approx. 450 – 720 patients

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

approx. 5 – 9 patients

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 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).

4. Treatment costs

Annual treatment costs:

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

and

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Axicabtagene ciloleucel[4]	€ 282,000.00
Additionally required SHI services[5]	€ 743.23

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 October 2022)

Other SHI services:

Designation of the therapy	Type of service	Cost per unit	Number per cycle	Number per patient/ year year	Cost per patient/ year 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

[4] It concerns only the cost of the medicinal product Yescarta.
[5] Since leukapheresis is part of the manufacture of the medicinal product pursuant to Section 4, paragraph 14 Medicinal Products Act (AMG), no further costs are incurred in this respect for the medicinal product to be assessed.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 3 November 2022.

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

Berlin, 3 November 2022

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

Prof. Hecken