Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Tisagenlecleucel (Reassessment after Expiry: B-cell Acute Lymphoblastic Leukaemia)

of 17 September 2020

At its session on 17 September 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. In Annex XII, the information on the benefit assessment of the active ingredient tisagenlecleucel (B-cell acute lymphoblastic leukaemia) of 7 March 2019 (Federal Gazette, BAnz AT 2 April 2019 B2) in the version of the resolution of 1 August 2019 (Federal Gazette, BAnz AT 27 August 2019 B8) is adopted as follows:

Resolution has been repealed

Courtesy translation – only the German version is legally binding.

“Tisagenlecleucel

Resolution of: 17 September 2020
Entry into force on: 17 September 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Approved therapeutic indication (according to the marketing authorisation of 23 August 2018):

Kymriah is indicated for the treatment of: Paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

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

Tisagenlecleucel is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (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).

Resolution has been repealed

Paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse

Extent of the additional benefit and significance of the evidence for tisagenlecleucel:

Hint for a non-quantifiable additional benefit because the scientific data does not permit quantification

Study results according to endpoints:[1]

Paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse

ELIANA study: single-arm, multi-centre Phase II study (data cut-off 1 July 2019, ITT population)

ENSIGN study: single-arm, multi-centre Phase II study (data cut-off 24 May 2019, ITT population)

[1] Data from the dossier assessment by the G-BA (published on 1 July 2020) unless otherwise indicated.

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Mortality

Endpoint	ELIANA		ENSIGN	
	N	Median survival time in months [95% CI] *Patients with event n (%)*	N	Median survival time in months [95% CI] *Patients with event n (%)*
Overall survival				
	97	n.a. [19,4; n.c.] *44 (45.6)*	75	25.9 [10.2; 37.7] *36 (48.0)*
		Kaplan-Meier estimator [95% CI]		Kaplan-Meier estimator [95% CI]
Study month 3	97	87.5 [79.0; 92.7]	75	88.7 [78.6; 94.2]
Study month 6	97	77.0 [67.1; 84.2]	75	78.7 [67.1; 86.5]
Study month 9	97	73.8 [63.7; 81.5]	75	68.6 [56.3; 78.1]
Study month 12	97	69.5 [59.2; 77.7]	75	59.9 [47.4; 70.3]
Study month 18	97	60.9 [50.3; 69.9]	75	-[a]
Study month 24	97	57.5 [46.9; 66.8]	75	-[a]

Morbidity

	ELIANA		ENSIGN	
	N	Response rate in % [95% CI] *Patients with event n (%)*	N	Response rate in % [95% CI] *Patients with event n (%)*
Response (CR/CRi) within 6 months[b]				
Total	97	68.0 [57.8; 77.1] *66 (68)*	75	60.0 [48.0; 71.1] *45 (60.0)*
CR	97	- *55 (56.7)*	75	- *38 (50.7)*
CRi	97	- *11 (11.3)*	75	- *7 (9.3)*

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	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*
Relapse-free survival[c]				
	66	n.a. [17,8; n.c.] *24 (36.4)*	45	n.a. [13,6; n.c.] *13 (28.9)*
		Percentage of patients with MRD-negative status [95% CI] *(%)*		Percentage of patients with MRD-negative status [95% CI] *(%)*
MRD negativity[d]				
	97	65 [56.7; 76.2] *(67.0)*	79	45 [54.3; 78.4] *(57.3)*
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*
EQ-5D VAS[e]				
No usable data				

Health-related quality of life

	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*
PedsQL[f]				
No usable data				

Side effects

Endpoint	**Chemotherapy lymphocyte depletion**		**Infusion of tisagenlecleucel up to Study week 8**		**Study week 9 to Study month 12**	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
Adverse events in total						
ELIANA	77	61 (79.2)	79	78 (98.7)	74	69 (93.2)
ENSIGN	61	51 (83.6)	64	63 (98.4)	56	46 (82.1)
Serious adverse events (SAE)						

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ELIANA	77	8 (10.4)	79	54 (68.4)	74	23 (31.1)
ENSIGN	61	9 (14.8)	64	46 (71.9)	56	21 (37.5)
Severe adverse events (CTCAE grade 3 or 4)[g]						
ELIANA	77	30 (39.9)	79	66 (83.5)	74	36 (48.7)
ENSIGN	61	38 (62.3)	64	54 (84.4)	56	26 (46.4)
Therapy discontinuation because of adverse events						
ELIANA	77	0	79	n.r.	74	n.r.
ENSIGN	61	0	64	n.r.	56	n.r.
Severe AE (CTCAE grade 3/4) with incidence ≥ 5% at the SOC level[g]						
Blood and lymphatic system disorders						
ELIANA	77	11 (14.3)	79	39 (49.4)	74	10 (13.5)
ENSIGN	61	18 (29.5)	64	38 (59.4)	56	7 (12.5)
Cardiac disorders						
ELIANA	77	-	79	8 (10.1)	74	-
ENSIGN	61	-	64	-	56	--
Gastrointestinal disorders						
ELIANA	77	-	79	14 (17.7)	74	-
ENSIGN	61	-	64	11 (17.2)	56	4 (7.1)
General disorders and administration site conditions						
ELIANA	77	-	79	11 (13.9)	74	-
ENSIGN	61	-	64	10 (15.6)	56	-
Hepatobiliary disorders						
ELIANA	77	-	79	6 (7.6)	74	-
ENSIGN	61	-	64	-	56	-
Immune system disorders						
ELIANA	77	-	79	42 (53.2)	74	4 (5.4)
ENSIGN	61	-	64	22 (34.4)	56	-
Infections and infestations						
ELIANA	77	5 (6.5)	79	19 (24.1)	74	20 (27.0)
ENSIGN	61	4 (6.6)	64	7 (10.9)	56	12 (21.4)
Investigations						
ELIANA	77	18 (23.4)	79	44 (55.7)	74	16 (21.6)
ENSIGN	61	26 (42.6)	64	44 (68.8)	56	12 (21.4)
Metabolism and nutrition disorders						
ELIANA	77	4 (5.2)	79	29 (36.7)	74	7 (9.5)
ENSIGN	61	8 (13.1)	64	24 (37.5)	56	4 (7.1)

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Musculoskeletal and connective tissue disorders						
ELIANA	77	-	79	5 (6.3)	74	-
ENSIGN	61	-	64	-	56	-
Nervous system disorders						
ELIANA	77	-	79	10 (12.7)	74	-
ENSIGN	61	-	64	5 (7.8)	56	-
Psychiatric disorders						
ELIANA	77	-	79	6 (7.6)	74	-
ENSIGN	61	-	64	-	56	-
Renal and urinary disorders						
ELIANA	77	-	79	9 (11.4)	74	-
ENSIGN	61	-	64	7 (10.9)	56	-
Respiratory, thoracic, and mediastinal disorders						
ELIANA	77	-	79	23 (29.1)	74	6 (8.1)
ENSIGN	61	4 (6.6)	64	12 (18.8)	56	3 (5.4)
Vascular disorders						
ELIANA	77	-	79	17 (21.5)	74	5 (6.8)
ENSIGN	61	4 (6.6)	64	16 (25.0)	56	-
Serious AE (SAE) with incidence ≥ 5%						
Blood and lymphatic system disorders (SOC)						
ELIANA	77	-	79	16 (20.3)	70	4 (5.4)
ENSIGN	61	-	64	23 (35.9)	56	5 (8.9)
Febrile neutropoenia (PT)						
ELIANA	77	-	79	13 (16.5)	70	-
ENSIGN	61	-	64	21 (32.8)	56	3 (5.4)
Cardiac disorders (SOC)						
ELIANA	77	-	79	5 (6.3)	70	-
ENSIGN	61	-	64	-	56	-
Gastrointestinal disorders (SOC)						
ELIANA	77	-	79	5 (6.3)	70	-
ENSIGN	61	-	64	5 (7.8)	56	-
General disorders and administration site conditions (SOC)						
ELIANA	77	-	79	5 (6.3)	70	5 (6.8)
ENSIGN	61	-	64	4 (6.3)	56	5 (8.9)
Pyrexia (PT)						
ELIANA	77	-	79	-	70	4 (5.4)

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ENSIGN	61	-	64	-	56	5 (8.9)
Immune system disorders (SOC)						
Cytokine release syndrome (PT)						
ELIANA	77	-	79	50 (63.3)	70	-
ENSIGN	61	-	64	41 (64.1)	56	-
Infections and infestations (SOC)						
ELIANA	77	-	79	11 (13.9)	70	16 (21.6)
ENSIGN	61	-	64	9 (14.1)	56	12 (21.4)
Metabolism and nutrition disorders (SOC)						
ELIANA	77	-	79	4 (5.1)	70	-
ENSIGN	61		64	3 (4.7)	56	
Musculoskeletal and connective tissue disorders (SOC)						
ENSIGN	61		64		56	3 (5.4)
Nervous system disorders (SOC)						
ELIANA	77	-	79	5 (6.3)	70	-
ENSIGN	61	-	64	9 (14.1)	56	-
Seizure (PT)						
ENSIGN	61	-	64	3 (4.7)	56	-
Encephalopathy (PT)						
ENSIGN	61	-	64	4 (6.3)	56	-
Renal and urinary disorders (SOC)						
ELIANA	77	-	79	5 (6.3)	70	-
ENSIGN	61	-	64	4 (6.3)	56	-
Acute kidney injury (PT)						
ELIANA	77	-	79	4 (5.1)	70	-
ENSIGN	61	-	64	3 (4.7)	56	-
Respiratory, thoracic and mediastinal disorders (SOC)						
ELIANA	77	-	79	10 (12.7)	70	6 (8.1)
ENSIGN	61	-	64	8 (12.5)	56	-
Hypoxia						
ENSIGN	61	-	64	4 (6.3)	56	-
Respiratory arrest						
ENSIGN	61	-	64	3 (4.7)	56	-
Vascular disorders (SOC)						
ELIANA	77	-	79	8 (10.1)	70	-
ENSIGN	61	-	64	8 (12.5)	56	-

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Hypotension (PT)						
ELIANA	77	-	79	8 (10.1)	70	-
ENSIGN	61	-	64	7 (10.9)	56	-

	Tisagenlecleucel infusion up to Study week 8		Study week 9 to Study week 12	
	N	Patients with event n (%)	N	Patients with event n (%)
AE of special interest (Group Term)				
Cytokine release syndrome				
ELIANA	79	61 (77.2)	74	no data available[h]
ENSIGN	64	50 (78.1)	56	no data available[h]
Haematopoietic cytopoenia persisting on Day 28				
ELIANA	79	33 (41.8)	74	no data available[i]
ENSIGN	64	27 (42.2)	56	no data available[i]
Infections				
ELIANA	79	34 (43.0)	74	40 (54.1)
ENSIGN	64	26 (40.6)	56	33 (58.9)
Prolonged B-cell depletion or agammaglobulinemia				
ELIANA	79	35 (44.3)	74	15 (20.3)
ENSIGN	64	27 (42.2)	56	8 (14.3)
Serious neurological event[j]				
ELIANA	79	31 (39.2)	74	5 (6.8)
ENSIGN	64	19 (29.7)	56	2 (3.6)
Tumour lysis syndrome				
ELIANA	79	4 (5.1)	74	1 (1.4)
ENSIGN	64	1 (1.6)	56	1 (1.8)

[a] Estimators for overall survival are presented only up to the duration of the median observation period
[b] Assessment by the IRC
[c] The response was estimated by the IRC. According to the study report, all relapses that were considered events were confirmed by the IRC. All patients who reached CR/CRi within 6 months according to the IRC represent the reference value.
[d] All patients who reached CR/CRi within 6 months according to the IRC represent the reference value.
[e] The return rate of the questionnaires was > 70% only for screening.
[f] The return rate to the questionnaires was < 70%.
[g] The pharmaceutical company presents AE for CTCAE grades 3 and 4 separately. The common presentation of the CTCAE grade 3/4 is done by own calculation. The graduation of the CRS was based on the PGS-CRS.
[h] No information available in primary result tables in the study report.

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[i] In accordance with operationalisation, cytopoenia persisting on Day 28 cannot occur from Study week 9 to Study month 12.
[j] According to the manufacturer's dossier, the designation of serious neurological events as AE of special interest was planned in close cooperation with the EMA (European Medicines Agency). These AE are based on the EU RMP.

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; EQ-5D VAS = Visual Analogue Scale of the European Quality of Life 5 Dimensions; PedsQL = Paediatric Quality of Life Inventory; CI = confidence interval; IRC = Independent Review Committee N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; n.r. not relevant; vs = versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	n.a.	not assessable
Morbidity	n.a.	not assessable
Health-related quality of life	n.a.	not assessable
Side effects	n.a.	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.a.: not assessable

Resolution has been repealed

2. Number of patients or demarcation of patient groups eligible for treatment

Paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse

approx. 50–65 patients

3. Requirements for a quality-assured application

The requirements in the product information and the Risk Management Plan (RMP) under the terms of the marketing authorisation are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) as well as the conditions or restrictions for the safe and effective use

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of Kymriah® (active ingredient: tisagenlecleucel) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 12 August 2020):

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

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide training material as well as a patient emergency card. The training material for all healthcare professionals who are to prescribe, deliver, and administer tisagenlecleucel 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 tocilizumab at the place of treatment, the provision of relevant information to patients, and the full and adequate reporting of side effects.

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

The resolution of 17 September 2020 on quality assurance measures for the application of CAR-T cells in B-cell neoplasia provides further details.

Resolution has been repealed

4. Treatment costs

Annual treatment costs:

Paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse

Designation of the therapy	Annual treatment costs/patient
Tisagenlecleucel[2,3]	€ 275,000.00
Additionally required SHI services:	
Lymphocyte depletion	€ 471.70 – 919.88

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 September 2020

[2] This relates exclusively to the costs of the medicinal product Kymriah®.

[3] 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.

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Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs per unit	Number per cycle	Number per patient per year	Costs per patient per year
Lymphocyte depletion					
Fludarabine	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4	4	€ 324
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	2	2	€ 162

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II. Entry into force

1. **The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 17 September 2020.**
2. **The period of validity of the resolution is limited to 1 September 2023.**

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

Berlin, 17 September 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken

Resolution has been repealed

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