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
Tisagenlecleucel (new therapeutic indication: follicular lymphoma, pretreated patients)

of 1 December 2022

At its session on 1 December 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. **In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Tisagenlecleucel in accordance with the resolution of 17 September 2020:**

Tisagenlecleucel

Resolution of: 1 December 2022
Entry into force on: 1 December 2022
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 29 April 2022):

Kymriah is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Therapeutic indication of the resolution (resolution of 1 December 2022):

See new therapeutic indication according to marketing authorisation.

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

Tisagenlecleucel is approved as a medicinal product for the treatment of rare diseases in accordance with 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).

<u>Adults with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy</u>

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

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

Study results according to endpoints:[1]

Adults with relapsed or refractory follicular lymphoma (FL) 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.a.	The data are not assessable.
Morbidity	n.a.	The data are not assessable.
Health-related quality of life	n.a.	The data are not assessable.
Side effects	n.a.	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

ELARA study: Uncontrolled phase II study, data cut-off from 03.08.2021

Mortality

Endpoint	**Enrolled set N = 98**
	Patients with event n (%)
Overall survival	
Data cut-off from 03.08.2021	10 (10.2)
Overall survival in month	**Kaplan-Meier estimator [95% CI]**
18	93.2 [85.5; 96.9]

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

Morbidity

Endpoint	Enrolled set N = 98	
Complete remission rate (presented additionally)	**IRC**	**Medical investigators[a]**
n (%) [95% CI]	67 68.3 [58; 77]	70 71.4 [61; 80]
EQ 5D-VAS		
There are no usable data.		

Health-related quality of life

Endpoint
FACT-Lym
There are no usable data.
SF-36
There are no usable data.

Side effects

Endpoint	Leukapheresis[b] N = 119	Before LDC[c] N = 98	LDC[c] N = 97	TL infusion up to W8 N = 96	W8 to 1 year after TL infusion N = 97	Later than 1 year after TL infusion[d] N = 85
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
AE	n.r.	76 (77.6)	75 (77.3)	94 (96.9)	81 (84.4)	28 (32.9)
AE CTCAE grade ≥ 3[e]	n.r.	33 (33.7)	37 (38.1)	69 (71.1)	43 (44.8)	13 (15.3)
SAE	n.r.	16 (16.3)	7 (7.2)	27 (27.8)	20 (20.8)	10 (11.8)
AE that led to discontinuation of study medication[f]	n.r.	1	–	–	–	–

AE **CTCAE grade ≥ 3 with incidence ≥ 5%** **SOC** *PT*	**Enrolment in the study up to LDC (Enrolled set)[h]** **N = 98** *n (%)*	**LDC up to TL infusion (Enrolled set)[h]** **N = 97** *n (%)*	**TL infusion up to W8 (TL infusion set)** **N = 97** *n (%)*	**> W8 up to 1 year after TL infusion (TL infusion set)** **N = 96** *n (%)*	**1 year after TL infusion or later (TL infusion set)** **N = 85[i]** *n (%)*
Blood and lymphatic system disorders[g]	**14 (14.3)**	**18 (18.6)**	**51 (52.6)**	**27 (28.1)**	**8 (9.4)**
Neutropenia	7 (7.1)	6 (6.2)	32 (33)	18 (18.8)	5 (5.9)
Anaemia	8 (8.2)	8 (8.2)	13 (13.4)	5 (5.2)	–
Thrombocytopenia	–	–	9 (9.3)	5 (5.2)	–
Febrile neutropenia	–	–	10 (10.3)	–	–
Lymphopenia	–	6 (6.2)	6 (6.2)	–	–
Leukopenia	–	–	7 (7.2)	–	–
Infections and infestations[g]	**–**	**–**	**–**	**5 (5.2)**	**–**
Pneumonia	–	–	–	5 (5.2)	–
Investigations	**5 (5.1)**	**11 (11.3)**	**24 (24.7)**	**10 (10.4)**	**–**
Leukopenia	–	5 (5.2)	12 (12.4)	7 (7.3)	–
Neutropenia	–	–	15 (15.5)	6 (6.3)	–
Thrombocytopenia	5 (5.1)	–	–	–	–
Lymphocytopenia	–	8 (8.2)	8 (8.2)	–	–
SAE **with incidence ≥ 5%**	**Enrolment in the study up to LDC (Enrolled set)[h]** **N = 98**	**LDC up to TL infusion (Enrolled set)[h]** **N = 97**	**TL infusion up to W8 (TL infusion set)** **N = 97**	**> W8 up to 1 year after TL infusion (TL infusion set)** **N = 96**	**1 year after TL infusion or later (TL infusion set)** **N = 85[i]**
SOC *PT*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Blood and lymphatic system disorders[g]	**–**	**–**	**5 (5.2)**	**–**	**–**
Febrile neutropenia	–	–	5 (5.2)	–	–
Infections and infestations	**–**	**–**	**–**	**6 (6.3)**	**–**
Pneumonia	–	–	–	6 (6.3)	–

Immune system disorders	–	–	**17 (17.5)**	–	–
Cytokine release syndrome	–	–	17 (17.5)	–	–
AEs of special interest	**Enrolment in the study up to LDC (Enrolled set) N = 98**	**LDC up to TL infusion (Enrolled set) N = 97**	**TL infusion up to W8 (TL infusion set) N = 97**	**> W8 up to 1 year after TL infusion (TL infusion set) N = 96**	**1 year after TL infusion or later (TL infusion set) N = 85**
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Subjects with at least one AESI regardless of severity grade	54 (55.1)	39 (40.2)	88 (90.7)	70 (72.9)	18 (21.2)
Subjects ≥ 1 serious AESI (identified/ potential)	8 (8.2)	4 (4.1)	25 (25.8)	16 (16.7)	7 (8.2)
Important identified risks					
Subjects with ≥ 1 severe AESI ≥ grade 3	28 (28.6)	34 (35.1)	68 (70.1)	41 (42.7)	11 (12.9)
Cytokine release syndrome	–	–	47 (48.5)	1 (1.0)	1 (1.2)
Haematological diseases including cytopenias	34 (34.7)	35 (36.1)	73 (75.3)	42 (43.8)	12 (14.1)
Infections	27 (27.6)	8 (8.2)	20 (20.6)	37 (38.5)	9 (10.6)
Prolonged B-cell depletion or agammaglobulinaemia	2 (2.0)	1 (1.0)	10 (10.3)	8 (8.3)	–
Serious neurologic events	2 (2.0)	2 (2.1)	10 (10.3)	2 (2.1)	–
Tumour Lysis Syndrome	2 (2.0)	2 (2.1)	1 (1.0)	1 (1.0)	–
Important potential risks					
Subjects with ≥ 1 severe AESI ≥ grade 3	–	1 (1.0)	–	3 (3.1)	1 (1.2)
Cerebral oedema	–	–	–	–	–
Secondary malignancies (including oligo/monoclonalit	–	–	–	4 (4.2)	2 (2.4)

y of the vector insertion site)					
Recurrence or deterioration of an autoimmune disease	3 (3.1)	2 (2.1)	12 (12.4)	10 (10.4)	1 (1.2)
Deterioration of the graft-versus-host response	–	–	–	1 (1.0)	–

[a] The assessment of the complete remission rate by medical investigators was performed as a sensitivity analysis.
[b] Assessment and presentation of AEs during leukapheresis was pre-specified in SAP.
[c] Not all (severe) AEs were recorded.
[d] The focus of data collection from month 12 onwards was on AESI.
[e] The severity grade of cytokine release syndrome (CRS) was assessed according to the revised grading system of Lee et al. (2014) [5]. For all other AEs, the severity grade was determined according to CTCAE (version 4.03) or, if an AE could be classified according to CTCAE, according to the severity of mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4) or fatal (grade 5).
[f] Since CAR-T cell therapy is administered as a single dose, this therapy cannot be discontinued after infusion.
[g] This AE is an AE of special interest.
[h] Only specific AEs (all infections, all clinical AEs grade ≥ 3 and all AEs related to the study procedure or leading to its discontinuation) were collected during this study period. Only specific SAEs should be collected.
[i] After month 12, only specific AEs were recorded that were observed in connection with the study medication were recorded.

Abbreviations used:
AESI = adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events; IRC = independent review committee; CI = confidence interval; KM = Kaplan Meier; LDC = lymphocyte depletion chemotherapy; N = number of patients evaluated; n = number of patients with (at least one) event; n.r. = not reported; n.a. = not achieved; PT = preferred term; SAP = statistical analysis plan; SOC = system organ class; SAE = serious adverse event; TL = tisagenlecleucel

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

Adults with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

approx. 650 – 690 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 Kymriah (active ingredient: tisagenlecleucel) at the following publicly accessible link (last access: 28 July 2022):

https://www.ema.europa.eu/en/documents/product-information/kymriah-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 tisagenlecleucel 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 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 tisagenlecleucel, and to carry the patient emergency card at all times.

Tisagenlecleucel must be used in a qualified treatment centre. For the infusion of tisagenlecleucel 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).

Patients with grade 3b follicular lymphoma were not investigated in the ELARA study. Grade 3b follicular lymphoma is treated in accordance with the generally accepted state of medical knowledge, analogous to diffuse large B-cell lymphoma (DLBCL). Tisagenlecleucel has a separate marketing authorisation for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

4. Treatment costs

Annual treatment costs:

Adults with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy

Designation of the therapy	Annual treatment costs/ patient
Tisagenlecleucel[2,3]	€ 265,000.00
Additionally required SHI services:	
Lymphocyte depletion	€ 395.40
Premedication	Incalculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 November 2022)

Other SHI services:

Designation of the therapy	Type of service	Unit cost	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	€ 100	3	3	€ 300
Cyclophosphamide	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 100	3	3	€ 300

5. Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with tisagenlecleucel

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients which, on the basis of the marketing authorisation under Medicinal Products Act, can be used in a combination therapy with tisagenlecleucel for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy:

<u>Adults with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy</u>

- No active ingredient that can be used in a combination therapy that fulfils the

[2] It concerns only the cost of the medicinal product Kymriah®.
[3] 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.

requirements of Section 35a, paragraph 3, sentence 4 SGB V.

II. Entry into force

1. **The resolution will enter into force on the day of its publication on the website of the G-BA on 1 December 2022.**
2. **The period of validity of the resolution is limited to 1 September 2028.**

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

Berlin, 1 December 2022

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

Prof. Hecken