Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-L):

Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Autologous anti-CD19-transduced CD3+ cells (mantle cell lymphoma, pretreated patients)

of 5 August 2021

At its session on 5 August 2021, 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 on DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient autologous anti-CD19-transduced CD3+ cells as follows:

Autologous anti-CD19-transduced CD3+ cells

Resolution of: 5 August 2021
Entry into force on: 5 August 2021
BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 14 December 2020):

Tecartus is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

Therapeutic indication of the resolution (resolution of 5 August 2021):

see therapeutic indication according to marketing authorisation.

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

Autologous anti-CD19-transduced CD3+ cells are approved as medicinal products 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 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).

<u>Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor</u>

Extend of the additional benefit and significance of the evidence of autologous anti-CD19 transduced CD3+ cells:

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

Study results according to endpoints:[1]

Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor

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	∅	There are no usable data for the benefit assessment.
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		

ZUMA-2 study: Non-controlled, multicentre Phase II study

Data cut-off from 31.12.2020, unless otherwise indicated

Mortality

Endpoint	Full Analysis Set N = 74
	Median survival time in months [95% CI] *Patients with event n (%)*
Overall survival	
Data cut-off 31.12.2020	NR [25.9; NE] *32 (43)*
Rate overall survival	Kaplan-Meier estimator (%) [95% CI]
at month 3	91.8 [82.7; 96.2]
at month 6	83.6 [72.9; 90.3]
at month 9	78.1 [66.8; 86.0]

[1]Data from the dossier assessment of the G-BA (published on the 17.05.2021) and from the amendment to the dossier assessment from 09.07.2021, unless otherwise indicated.

at month 12	76.7 [65.3; 84.8]
at month 18	68.5 [56.5; 77.8]
at month 24	64.4 [52.3; 74.2]
at month 30	58.1 [45.7; 68.8]
at month 36	55.0 [41.9; 66.4]
at month 42	52.0 [38.3; 64.0]

Morbidity

Complete response as "Best Objective Response"		
	N	n (%) [95% CI]
Individuals with CR as assessed by medical investigators		
Data cut-off 31.12.2020	74	46 (62) [50.1; 73.2]
Progression-free survival[a]		
	N	Median time to event in months [95% CI] *Patients with event n (%)*
	74	19.1 [9.9; 38.2] *38 (51)*
EQ 5D-VAS[b]		
	N	*Patients with event n (%)* Mean difference [95% CI] Median (min; max)
Baseline	74	*67 (90.5)* 81.7 [77.9; 85.5] 85.0 [45.0; 100.0]
Week 4 Changes from baseline	74	*50 (73.5)* -7.8 [-12.8; -2.7] -
Month 3 Changes from baseline	74	*53 (82.8)* -2.4 [-7.0; 2.3] -
Month 6 Changes from baseline	74	*53 (62.5)* - -

Health-related quality of life

There are no data.

Side effects[c]

Endpoint	After KTE-X19 infusion mITT/safety population	
	N	Patients with event n (%)
Adverse events (AE) in total		
	68	68 (100)
Serious adverse events (SAE)		
	68	48 (71)
Severe adverse events (CTCAE grade ≥ 3)[d]		
	68	67 (99)
AE, which led to the discontinuation of the study medication		
	68	-[e]
SAE with incidence ≥ 5 % after PT **SOC** PT		
Nervous system disorders	68	20 (29)
Encephalopathy	68	12 (18)
Infections and infestations	68	21 (31)
Pneumonia	68	11 (16)
Sepsis	68	4 (6)
General disorders and administration site conditions	68	15 (22)
Fever	68	14 (21)
Vascular disorders	68	13 (19)
Hypotension	68	11 (16)
Respiratory, thoracic and mediastinal disorders	68	10 (15)
Hypoxia	68	7 (10)
Respiratory failure	68	4 (6)
Investigations	68	7 (10)
Blood and lymphatic system disorders	68	6 (9)
Anaemia	68	4 (6)
Psychiatric disorders	68	6 (9)
Confusion	68	5 (7)

Renal and urinary disorders	68	6 (9)
Acute kidney injury	68	5 (7)
Cardiac disorders	68	4 (6)
Gastrointestinal disorders	68	5 (7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	68	5 (7)
Severe AE CTCAE grade ≥ 3 with incidence ≥ 5 % according to SOC and PT [d] **SOC** PT		
General disorders and administration site conditions	68	14 (21)
Fever	68	9 (13)
Blood and lymphatic system disorders	68	53 (78)
Anaemia	68	35 (51)
Neutropenia	68	23 (34)
Thrombocytopenia	68	11 (16)
Leukopenia	68	10 (15)
Febrile neutropenia	68	5 (7)
Lymphopenia	68	4 (6)
Metabolism and nutrition disorders	68	30 (44)
Hypophosphataemia	68	15 (22)
Hyponatremia	68	7 (10)
Hypokalaemia	68	5 (7)
Hypocalcaemia	68	4 (6)
Investigations	68	42 (62)
Neutrophil counts decreased	68	36 (53)
Platelet counts decreased	68	26 (38)
Leukocytes counts decreased	68	28 (41)
Alanine aminotransferase increased	68	6 (9)
Aspartate aminotransferase increased	68	7 (10)
Lymphocyte counts decreased	68	6 (9)
Gastrointestinal disorders	68	9 (13)
Vascular disorders	68	**22 (32)**
Hypotension	68	15 (22)
Hypertension	68	9 (13)
Nervous system disorders	68	19 (28)

Encephalopathy	68	12 (18)
Respiratory, thoracic and mediastinal disorders	68	18 (26)
Hypoxia	68	14 (21)
Lung failure	68	4 (6)
Cardiac disorders	68	-
Infections and infestations	68	23 (34)
Pneumonia	68	10 (15)
Sepsis	68	4 (6)
Psychiatric disorders	68	10 (15)
State of confusion	68	8 (12)
Musculoskeletal and connective tissue disorders	68	4 (6)
Renal and urinary disorders	68	6 (9)
Acute kidney injury	68	5 (7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	68	6 (9)
Adverse Events of special interest		
Identified risks		
Cytokine release syndrome	68	62 (91)
Neurologic events	68	43 (63)
Cytopenias (thrombocytopenia, neutropenia, anaemia)	68	65 (96)
Infections	68	36 (53)
Hypogammaglobulinemia	68	14 (21)
Potential risks		
Immunogenicity[f]	68	n. d.
Secondary malignancies[f]	68	n. d.
Replication-competent retroviruses	68	0
Tumour Lysis Syndrome	68	1 (1)

[a] Data from statement
[b] Data cut-off 24.07.2019
[c] After infusion, AEs were fully recorded only in the post-treatment phase. This lasted for 3 months or until disease progression and consequent withdrawal from the post-treatment phase. In the subsequent long-term follow-up phase, only specific AE/SAEs were recorded for 24 months after treatment with KTE-X19 or until disease progression, whichever occurs first
[d] The severity of cytokine release syndrome was assessed according to the revised grading system of Lee et al. (2014). For all other AEs, severity was determined using CTCAE (version 4.03).
[e] AEs leading to study termination are no longer possible after administration of the CAR-T cell infusion
[f] The pharmaceutical company states that the AEs of special interest immunogenicity and secondary malignancy were only considered in the primary analysis. No data on the present data cut-off is available.

Abbreviations used:

CTCAE =Common Terminology Criteria for Adverse Events; CR = Complete response; EQ-5D VAS: Visual analogue scale of the EuroQol-5 dimension; FAS: full analysis set; HR = hazard ratio; CI = confidence interval; mITT: modified intention-to-treat; N = number of patients evaluated; n = number of patients with (at least one) event; NR = not reached; NE = not assessable; vs = versus

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

Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor

approx. 105 to 150 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 Tecartus (active ingredient: autologous anti-CD19-transduced CD3+ cells) at the following publicly accessible link (last access: 24 June 2021):

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

This medicinal product has been authorised under a so-called "conditional approval" scheme. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency (EMA) will assess new information on this medicinal product at least annually and update the product information for healthcare professionals as necessary.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient emergency card. Training materials for all healthcare professionals who will prescribe, dispense, and administer autologous anti-CD19-transduced CD3+ cells include 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 autologous anti-CD19-transduced CD3+ cells, and to carry the patient emergency card at all times.

The parallel application resolution of 5 August 2021 clarifies that the resolution of 17 September 2020 on quality assurance measures for the use of CAR-T cells in B-cell neoplasms also applies in the context of infusions of autologous anti-CD-19-transduced CD3+ cells in B-cell lymphomas with the diagnosis C83.1 according to ICD-10-GM-2021.

4. Treatment costs

Treatment costs:

Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor

Designation of the therapy	Treatment costs/ patient[2]
Medicinal product to be assessed:	
Autologous anti-CD19-transduced CD3+ cells[3,4,5]	€ 360,000.00
additionally required SHI services	€ 779.61

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 15 July 2021)

Other SHI services:

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

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 5 August 2021.

[2] Autologous anti-CD19-transduced CD3+ cells is administered once.
[3] Information from the pharmaceutical company on the delivery price from module 3 of the dossier.
[4] It concerns only the cost of the medicinal product
[5] Since leukapheresis is part of the manufacture of the medicinal product pursuant to Section 4, 14, of the German Medicines Act (AMG), no further costs are incurred in this respect for the medicinal product to be assessed.

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

Berlin, 5 August 2021

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

Prof. Hecken