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
Exagamglogene autotemcel (β-thalassaemia, transfusion-dependent, ≥ 12 years, no HLA-matched related stem cell donor available)

of 3 July 2025

At their session on 3 July 2025, 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 shall be amended in alphabetical order to include the active ingredient Exagamglogene autotemcel as follows:

Exagamglogene autotemcel

Resolution of: 3 July 2025
Entry into force on: 3 July 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 9 February 2024):

Casgevy is indicated for the treatment of transfusion-dependent β-thalassemia (TDT) in patients 12 years of age and older for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.

Therapeutic indication of the resolution (resolution of 3 July 2025):

See therapeutic indication according to marketing authorisation.

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

Exagamglogene autotemcel 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 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 Ordinance on the Benefit Assessment of Pharmaceuticals (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).

Patients 12 years of age and older with transfusion-dependent β-thalassaemia for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related stem cell donor is not available

Extent of the additional benefit and significance of the evidence of exagamglogene autotemcel:

Indication of a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints:[1]

Patients 12 years of age and older with transfusion-dependent β-thalassaemia for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related stem cell donor is not available

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	↑↑	Advantage in the endpoint of transfusion independence
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable data.
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 ∅: No data available. n.a.: not assessable		

CLIMB-TDT-111: single-arm, open-label, multicentre phase I/II/III study and

CTX001-131: extension study;

5th data cut-off from 02.01.2025

Indirect comparison: Naïve comparison of the CLIMB-TDT-111 and CTX001-131 studies with data from the WebTHAL database of patients with natural course of disease and standard of care (endpoint of transfusion independence).

Mortality

Endpoint	Exagamglogene autotemcel	
	N[a]	*Patients with event n (%)*
Deaths	59	No deaths occurred.

[1] Data from the dossier evaluation of the G-BA (published on 15. April 2025), and from the amendment to the dossier assessment from 13 June 2025, unless otherwise indicated.

Morbidity

Endpoint	Exagamglogene autotemcel	
	N[a]	*Patients with event n (%)*
Transfusion independence		
Transfusion independence for 12 months[e]	59	53 (89.8)

Naïve indirect comparison Endpoint	Exagamglogene autotemcel		WebTHAL (standard of care)		Intervention vs control
	N[a]	*Patients with event n (%) [95% CI][b]*	N	*Patients with event n (%) [95% CI]*	RR [95% CI][c]; p value[d]
Transfusion independence					
Transfusion independence for 12 months[e]	59	53 (89.8) [79.2; 96.2]	54	0 (0)	98.1 [6.20; 1550.6]; < 0.0001

Endpoint	Exagamglogene autotemcel	
	N[a]	*Patients with event n (%)*
Health status using EQ-5D-VAS (≥ 18 to ≤ 35 years)		
- Improvement at month 24	39	7 (17.9)
Health status using EQ-5D-VAS (≥ 12 to < 18 years)		
- Improvement at month 24	20	2 (10.0)

Health-related quality of life

Endpoint	Exagamglogene autotemcel	
	N[a]	*Patients with event n (%)*
Paediatric Quality of Life Inventory (PedsQL) "Teen version"		
- Total score (improvement at month 24)	20	7 (35.0)
- Physical health (improvement at month 24)	20	7 (35.0)

- Psychosocial health (improvement at month 24)	20	4 (20.0)
Functional Assessment of Cancer Therapy – Bone Marrow Transplantation (FACT-BMT) *(presented additionally)*		
- FACT-BMT total score (improvement at month 24)	39	9 (23.1)
- FACT-G total score (improvement at month 24)	39	8 (20.5)
- BMTS (improvement at month 24)	39	10 (25.6)

Side effects

Endpoint MedDRA system organ classes	**Exagamglogene autotemcel**	
	N[a]	Patients with event n (%)[f]
Adverse events in total *(presented additionally)*	59	58 (98.3)
Serious adverse events (SAE)	59	26 (44.1)
Severe adverse events (CTCAE grade 3 or 4)	59	52 (88.1)
Therapy discontinuation due to adverse events	59	0 (0)
Severe adverse events according to MedDRA system organ class (with an incidence ≥ 10%)		
Blood and lymphatic system disorders	59	**42 (71.2)**
Febrile neutropenia	59	34 (57.6)
Anaemia	59	25 (42.4)
Thrombocytopenia	59	18 (30.5)
Neutropenia	59	7 (11.9)
Gastrointestinal disorders	59	**33 (55.9)**
Stomatitis	59	24 (40.7)
Nausea	59	7 (11.9)
Investigations	59	**27 (45.8)**
Thrombocytopenia	59	22 (37.3)
Neutropenia	59	17 (28.8)
Leukopenia	59	8 (13.6)
General disorders and administration site conditions	59	**20 (33.9)**
Mucositis	59	17 (28.8)
Metabolism and nutrition disorders	59	**22 (37.3)**
Loss of appetite	59	12 (20.3)
Hyperphosphatemia	59	6 (10.2)

Endpoint MedDRA system organ classes	**Exagamglogene autotemcel**	
	N[a]	Patients with event n (%)[f]
Hypokalaemia	59	8 (13.6)
Infections and infestations	59	**16 (27.1)**
Respiratory, thoracic and mediastinal disorders	59	**14 (23.7)**
Epistaxis		8 (13.6)
Hepatobiliary disorders	59	**8 (13.6)**
Liver disease with venous occlusion	59	6 (10.2)
Injury, poisoning and procedural complications	59	**6 (10.2)**
SAEs according to MedDRA system organ class (with an incidence ≥ 10%)		
Infections and infestations	59	**15 (25.4)**
Hepatobiliary disorders	59	**6 (10.2)**
Respiratory, thoracic and mediastinal disorders	59	**6 (10.2)**

a. Corresponds to the ITT (enrolled set) and the safety population.
b. Two-sided 95% CIs are calculated using the exact Clopper-Pearson method.
c. Own calculation of the RR and two-sided 95% CI (asymptotic). Application of a correction factor (addition of 0.5 in both study arms) in the case of 0 events in one study arm.
d. Own calculation of the p value using unconditional exact tests (z-pooled).
e. Transfusion independence for at least 12 (TI12) consecutive months after the Exa-Cel infusion with a simultaneously weighted average Hb value ≥ 9 g/dl. The evaluation begins 60 days after the last RBC transfusion administered for post-treatment of the Exa-Cel infusion (non-TDT-related) or for treatment of the TDT disease.
f. Admission until month 24

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; ITT: Intention-To-Treat; CI: confidence interval; MedDRA:: Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with (at least one) event; PES: Primary Efficacy Set; (S)AE: (serious) adverse event; TI12/6: transfusion independence for at least 12 or 6 months

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

Patients 12 years of age and older with transfusion-dependent β-thalassaemia for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related stem cell donor is not available

Approx. 20 – 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 Casgevy (active ingredient: exagamglogene autotemcel)

agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 24 June 2025):

https://www.ema.europa.eu/en/documents/product-information/casgevy-epar-product-information_en.pdf

Treatment with exagamglogene autotemcel should only be initiated and monitored by specialists who are experienced in the treatment of patients with β-thalassemia. Exagamglogene autotemcel must be used in a qualified treatment facility.

The quality assurance measures according to the ATMP Quality Assurance Guideline apply to the use of ATMP exagamglogene autotemcel in the therapeutic indication of β-thalassemia. Further details are regulated in Annex VI "Exagamglogene autotemcel in β-thalassemia and sickle cell disease" of the ATMP Quality Assurance Guideline.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (including patient identification card).

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient identification card. The training material for health professionals who prescribe, use or supervise the use of exagamglogene autotemcel includes information on the important identified risk of delayed platelet engraftment and the important potential risks of neutrophil engraftment failure and oncogenesis associated with genome editing and how to minimise these risks. It also contains instructions on how to provide the patient identification card and the guideline for patients.

The guideline for patients is intended to explain the risks and benefits of exagamglogene autotemcel treatment, the limited data on long-term effects, the signs of low platelet or leucocyte counts and blood cancers, as well as the need to report symptoms immediately to the treating doctor and to always carry the patient identification card with them.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

4. Treatment costs

Annual treatment costs:

Patients 12 years of age and older with transfusion-dependent β-thalassaemia for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related stem cell donor is not available

Designation of the therapy	Treatment costs/ patient[2]
Medicinal product to be assessed:	
Exagamglogene autotemcel	€ 2,200,000
Additionally required SHI services	€ 2,448.92 - € 3,661.58

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2025)

Other SHI services:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Busulfan	Surcharge for the production of a parenteral preparation containing cytostatic agents	€ 100	4	4	€ 400

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Patients 12 years of age and older with transfusion-dependent β-thalassaemia for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related stem cell donor is not available

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

[2] Exagamglogene autotemcel is used once only.

6. Percentage of study participants at study centres within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product Casgevy is a medicinal product placed on the market from 1 January 2025.

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed who participated at study sites within the scope of SGB V (German Social Security Code) is ≥ 5% of the total number of study participants.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore conducted to a relevant extent within the scope of SGB V.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 3 July 2025.

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

Berlin, 3 July 2025

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

Prof. Hecken