Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of all reimbursable medicinal products with new active ingredients.

For medicinal products approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to 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. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at their session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at their session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit

assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient exagamglogene autotemcel on 15 January 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 14 January 2025.

Exagamglogene autotemcel for the treatment of transfusion-dependent β-thalassaemia in patients 12 years of age and older 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.

Exagamglogene autotemcel concerns a gene therapy within the meaning of Section 4, paragraph 9 Medicinal Products Act.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 April 2025 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA adopted their resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G12-01) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA have evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance

with the General Methods [1] was not used in the benefit assessment of exagamglogene autotemcel.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Exagamglogene autotemcel (Casgevy) in accordance with the product information

Treatment of transfusion-dependent β-thalassaemia in patients 12 years of age and older for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen-matched related HSC donor is not available.

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

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of exagamglogene autotemcel is assessed as follows:

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

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

Justification:

The pharmaceutical company presented the results of the pivotal, single-arm, open-label, multicentre phase I/II/III CLIMB-TDT-111 study and the CLIMB-CTX001-131 extension study for the benefit assessment of exagamglogene autotemcel for the treatment of transfusion-dependent β-thalassaemia (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.

The study is divided into 4 phases: Phase 1 involves screening and pre-mobilisation, phase 2 involves mobilisation and harvesting of autologous CD34+ stem cells as well as production of exagamglogene autotemcel, phase 3 involves myeloablative conditioning and infusion of exagamglogene autotemcel, and phase 4 involves follow-up for 24 months. After successful completion of the study, a transition to the CLIMB-CTX001-131 extension study was possible.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

59 patients aged 12 up to and including 35 years with a confirmed diagnosis of transfusion-dependent β-thalassaemia (TDT) and for whom allogeneic SCT is appropriate but for whom no matched or related stem cell donor is available (ITT population) were enrolled in the study.

Of these, 56 patients received an infusion of exagamglogene autotemcel (Full Analysis Set (FAS)). For the evaluation of efficacy endpoints, the pharmaceutical company analysed 54 patients who were observed for at least 16 months after infusion and for at least 14 months after completion of RBC transfusions for post-transplant support or treatment of TDT disease (Primary Efficacy Set (PES)).

The time from therapy initiation (start of mobilisation) to the infusion of exagamglogene autotemcel is considered an essential part of the treatment. The ITT population is therefore used for the benefit assessment.

The primary efficacy endpoint was transfusion avoidance for at least 12 or 6 months. In addition, other endpoints in the categories of morbidity, health-related quality of life and side effects were assessed.

The benefit assessment was based on the 2nd data cut-off from 16 April 2023, as subsequently requested by the EMA. Within the framework of the written statement procedure, the pharmaceutical company subsequently submitted the 5th data cut-off from 2 January 2025. The following results relate to the current data cut-off.

Indirect comparisons

In addition to the results of the pivotal studies, the pharmaceutical company also presented two non-randomised, indirect comparisons. These include an indirect comparison with the randomised controlled Believe study versus luspatercept as well as an indirect, naïve comparison with the patient-individual data from the WebTHAL database.

The indirect comparison with the Believe study cannot be used for the benefit assessment due to different lengths of time in the comparison of transfusion independence (3 months in the Believe study vs 6 months in the CLIMB-TDT-111) and other systematic differences in the inclusion and exclusion criteria, e.g. in the age range of the patients enrolled.

The base population of the WebTHAL database comprises 831 patients with TDT, of which 268 patients were between 12 and 35 years of age and the data collection period was between 2016 and 2019. 54 were enrolled in an indirect comparison with the CLIMB study. The patients received regular RBC transfusions as standard of care and no subject was treated with luspatercept. There are limitations with regard to potential systematic differences between the study populations of the WebTHAL database and the CLIMB study due to different selection criteria, differences in baseline characteristics and with regard to the different start of the observation period.

On the results:

<u>Mortality</u>

Deaths were collected as safety events in the CLIMB-TDT-111 study. No death occurred at the time of the relevant data cut-off.

Morbidity

Transfusion independence

Transfusion-dependent β-thalassaemia is based on anaemia caused by the significantly reduced production of functional β-globin, which requires frequent and lifelong RBC transfusions. The required transfusions can lead to increasing iron overload of the organs and subsequent long-term complications in the patients despite iron elimination therapy. A long-term or sustainable avoidance of transfusions (transfusion independence) while maintaining a defined minimum value of haemoglobin represents a therapeutic goal of higher priority in the present therapeutic indication, with which a control of anaemia and anaemia-related symptoms is achieved, while avoiding RBC transfusions.

With regard to the evaluations of the different periods of transfusion independence, transfusion independence for ≥ 24 weeks is considered to be the relevant period in the present assessment for assuming long-term avoidance of transfusions (transfusion independence). Thus, transfusion independence for ≥ 24 weeks may represent a patient-relevant endpoint in the present therapeutic indication.

Transfusion independence was defined in the study as the percentage of patients who did not receive any RBC transfusions for at least 12 or 6 consecutive months after the exagamglogene infusion and had a weighted average haemoglobin value ≥ 9 g/dl.

In the CLIMB-TDT-111 study, transfusion independence was identified in 53 of 59 (89.8%) patients in the ITT population after 12 months at the time of the current data cut-off.

Due to the known natural course of the disease, it cannot be assumed that patients suffering from transfusion-dependent β-thalassemia will spontaneously reach clinically relevant higher haemoglobin levels in the natural course of their disease and/or become independent of regular transfusions with red blood cell concentrates.

In this respect, the result on transfusion independence achieved in the CLIMB-TDT-111 study after 12 months is considered a dramatic effect of the treatment compared to the expected natural course of the disease.

Against this background, the results of the presented naïve indirect comparison with data from the WebTHAL database of patients with natural course of disease or under treatment with "standard of care" are also used for the present assessment despite the limitations mentioned and taking into account the high effect magnitude.

The overall assessment showed a relevant advantage for treatment with exagamglogene autotemcel for the endpoint of transfusion independence.

However, it is not possible to estimate the extent to which the transfusion independence shown by the majority of patients leads to the avoidance of complications that may result from the regular transfusions with red blood cell concentrates that have already taken place. In particular, it remains unclear to what extent iron chelation therapy is still necessary for patients who have achieved transfusion independence. These uncertainties could also not be dispelled by the documents subsequently submitted by the pharmaceutical company.

Health status using EQ-5D-VAS

The visual analogue scale of the European Quality of Life 5-Dimension (EQ-5D-VAS) collects the self-assessment of the general health status. The study participants rated their health status on a vertical scale with scores ranging from 100 ("best perceivable health status") to 0 ("worst perceivable health status"). The youth version of the VAS is identical to the adult VAS.

The value at baseline is defined as the last non-missing measurement (planned or unplanned) prior to mobilisation. Responder analyses on the improvement or deterioration of the relevant threshold of 15% are available.

In 7 patients in the age group from ≥ 18 to ≤ 35 years and in 2 patients in the age group from ≥ 12 to < 18 years, an improvement of 15% was achieved at month 24.

Since no comparator data are available, no statements on the extent of the additional benefit can be derived from the results of the endpoint of health status using the EQ-5D-VAS.

Quality of life

FACT-BMT

The "Functional Assessment of Cancer Therapy – Bone Marrow Transplantation" (FACT-BMT) is a questionnaire for self-assessment of health-related quality of life for subjects who have received a bone marrow transplant. The FACT-BMT consists of the "Functional Assessment of Cancer Therapy – General" (FACT-G) and the "Bone Marrow Transplantation Subscale" (BMTS), which assesses treatment-specific aspects of bone marrow transplantation. The FACT-BMT consists of 5 categories with a total of 50 questions, the following domains were assessed: Physical well-being (PWB), social/ family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), bone marrow transplantation subscale (BMTS)

Using a 5-point Likert scale from 0 to 4, a component with a reference period of 7 days is surveyed. In scoring, a higher score means a higher quality of life. According to the information provided by the pharmaceutical company, the global scale was transformed from 0 to 200. The value at baseline is defined as the last non-missing measurement (planned or unplanned) prior to mobilisation.

The FACT-BMT total score showed an improvement by 15% at month 24 in 9 patients, the FACT-G total score in 8 patients and the BMTS in 10 patients.

There are uncertainties regarding the transferability of the FACT-BMT, which was developed for patients with cancer, to the study population with β-thalassaemia. Due to the existing uncertainties, the endpoint is presented additionally in the benefit assessment.

PedsQL

The PedsQL surveys the general health-related quality of life in children and adolescents and was used in the CLIMB-TDT-111 study as a teen version in study participants aged 12 to 18 years. The questionnaire consists of four multi-dimensional scales (physical, emotional, social and school functioning) and 3 summative scores (total score, physical health summative score, psychosocial health summative score). The questionnaire consists of a Likert scale from 1 to 4

(1 = best function [never] to 4 = worst function [always]); the values are then transformed into a scale from 1 to 100. Higher scores indicate a higher quality of life.

The value at baseline is defined as the last non-missing measurement (planned or unplanned) prior to mobilisation in the study. Responder analyses on the improvement or deterioration with the relevant 15% threshold are available.

The PedsQL Teen showed an improvement by 15% at month 24 in the total score in 7 patients, in the "physical health" domain in 7 patients and in the "psychosocial health" domain in 4 patients.

As no comparator data are available, no statements can be made about changes in quality of life as measured by PedsQL and FACT-BMT. In summary, no statements on the extent of the additional benefit can therefore be derived from the results on the quality of life endpoints.

Side effects

No study discontinuations due to adverse events were observed in the studies presented.

Adverse events (AEs) occurred in almost all patients in the studies. Severe AEs of grade ≥ 3 occurred in 88.1% of patients. In particular, these were AEs in the system organ classes "Blood and lymphatic system disorders", "Gastrointestinal disorders", "Investigations", "Metabolism and nutrition disorders", "General disorders and administration site conditions" and "Infections and infestations". Haematological and gastrointestinal side effects are characteristic of myeloablative therapy carried out prior to the administration of exagamglogene autotemcel. Serious AEs (SAEs) occurred in 44.1% of patients.

A conclusive assessment of the side effect profile of exagamglogene autotemcel is not possible due to the limited data on long-term safety and the lack of comparator data. Statements on the long-term side effect profile cannot be made without long-term data on the safety profile.

As no comparator data are available, no conclusive statements on the extent of the additional benefit can be derived from the data on side effects.

Overall assessment

Data from the pivotal, single-arm, open-label, multicentre phase I/II/III CLIMB-TDT-111 study, the CLIMB-CTX001-131 extension study as well as a naïve indirect comparison with the data from the WebTHAL database on the endpoint of transfusion independence were presented for the benefit assessment of exagamglogene autotemcel for the treatment of transfusion-dependent β-thalassaemia (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.

The data presented provides results on mortality, morbidity, quality of life and side effects. With the exception of the endpoint of transfusion independence, no statements on the extent of the additional benefit can be derived for any patient-relevant endpoint assessed in the studies due to a lack of comparator data.

In this respect, the result on transfusion independence achieved in the CLIMB-TDT-111 study after 12 months is considered a dramatic effect of the treatment compared to the expected natural course of the disease. Against this background, the results of the presented naïve indirect comparison with data from the WebTHAL database of patients with natural course of

disease or under treatment with "standard of care" are also used for the present assessment despite the limitations mentioned and taking into account the high effect magnitude.

The overall assessment showed a relevant advantage for the endpoint of transfusion independence. The data for the other patient-relevant endpoints cannot be assessed as no comparator data are available. Thus, no statements on the extent of the additional benefit of exagamglogene autotemcel can be derived for these endpoints and no consideration of the advantage related to transfusion independence can be made in the overall assessment.

As a result, a non-quantifiable additional benefit of exagamglogene autotemcel is identified since the scientific data does not allow quantification.

Significance of the evidence

The benefit assessment is based on the results of the single-arm, open-label CLIMB-TDT-111 study and the CLIMB-CTX001-131 extension study as well as the naïve indirect comparison with data from the WebTHAL database for the endpoint of transfusion independence.

Taking into account the sufficiently long duration of observation, particularly with regard to the safety and efficacy endpoints, as well as the results of the naïve indirect comparison in conjunction with a high effect magnitude, the significance of the evidence is classified as an indication despite the existing limitations of the data basis.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Casgevy with the active ingredient exagamglogene autotemcel. Casgevy was approved under "exceptional circumstances" as an orphan drug.

The therapeutic indication assessed here is as follows: Treatment of transfusion-dependent β-thalassaemia in patients 12 years of age and older for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen-matched related HSC donor is not available.

For the benefit assessment, the pharmaceutical company presented the results of the pivotal, single-arm, open-label, multicentre phase I/II/III CLIMB-TDT-111 study and the CLIMB-CTX001-131 extension study as well as two indirect comparisons for the endpoint of transfusion independence.

The data presented provides results on mortality, morbidity, quality of life and side effects. With the exception of the endpoint of transfusion independence, no statements on the extent of the additional benefit can be derived for any patient-relevant endpoint assessed in the studies due to a lack of comparator data.

In this respect, the result on transfusion independence achieved in the CLIMB-TDT-111 study after 12 months is considered a dramatic effect of the treatment compared to the expected natural course of the disease. Against this background, the results of the presented naïve indirect comparison with data from the WebTHAL database of patients with natural course of disease or under treatment with "standard of care" are also used for the present assessment despite the limitations mentioned and taking into account the high effect magnitude.

The overall assessment showed a relevant advantage for the endpoint of transfusion independence. The data for the other patient-relevant endpoints cannot be assessed as no comparator data are available. Thus, no statements on the extent of the additional benefit of exagamglogene autotemcel can be derived for these endpoints and no consideration of the advantage related to transfusion independence can be made in the overall assessment.

In the overall assessment, a non-quantifiable additional benefit is identified since the scientific data basis does not allow quantification.

The significance of the evidence is categorised as an indication.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The procedure of the pharmaceutical company is mathematically comprehensible in general. Uncertainties exist in particular due to the sources used to operationalise the transfusion dependence, the lack of age restriction, the lower limit from the registry data and the percentage values of HLA-identical sibling donors. Due to the uncertainties, IQWiG's own calculation including the data from the previous benefit assessment procedure of luspatercept[2] in the same therapeutic indication is used, which leads to a higher upper limit and a broader range of patients in the SHI target population.

2.3 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: 25 March 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-thalassaemia. 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).

[2] https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/574/

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.

2.4 Treatment costs

The treatment costs are based on the data of the product information and the data of the pharmaceutical company on the dispensing price from module 3 of the dossier.

Exagamglogene autotemcel is only dispensed to appropriately qualified inpatient treatment facilities. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the sales price of the pharmaceutical company, in deviation from the usually taken into account data of the LAUER-TAXE®.

Exagamglogene autotemcel is administered as a single intravenous infusion according to the specifications in the product information.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Exagamglogene autotemcel	Single dose	1	1	1

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Exagamglogene autotemcel	3 x 10^6 CD34+ cells/kg BW	3 x 10^6 CD34+ cells/kg BW	1 single infusion bag	1	1 single infusion bag

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)[3]	Value-added tax[4]	Costs
Medicinal product to be assessed				
Exagamglogene autotemcel	1 single infusion bag	€ 2,200,000	-	€ 2,200,000

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Exagamglogene autotemcel is a cell product produced from autologous CD34+ stem cells. Therefore, HSC mobilisation and leukapheresis are usually necessary to obtain the cell material. Since HSC mobilisation and leukapheresis are part of the manufacture of the medicinal product pursuant to Section 4, paragraph 14 of the Medicinal Products Act (AMG), no further costs are incurred in this respect for the medicinal product to be assessed.

Prior to treatment with Casgevy, complete myeloablative conditioning must be carried out according to the product information. The conditioning regimen used in the clinical study and listed in the product information was carried out with busulfan.

The planned intravenously administered busulfan dose was 3.2 mg/kg/day once daily or 0.8

[3] Information from the pharmaceutical company on the delivery price from module 3 of the dossier.
[4] According to the information provided by the pharmaceutical company, the medicinal product is exempt from value added tax.

mg/kg every 6 hours for 4 consecutive days. When administered once daily, the recommended AUC target range (0 - 24 h) was 4,500 – 5,500 µM*min and when administered every 6 hours, the AUC target range (0 – 6 h) was 900 – 1,350 µM*min.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were used as a basis (average body weight: Adults = 77.7 kg[5]; 12-year-olds = 47.1 kg[6]).

Patients should be tested for hepatitis B, hepatitis C and HIV infection prior to starting treatment with exagamglogene autotemcel.

Diagnostics to rule out chronic hepatitis B requires sensibly coordinated steps[7]. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. In certain case constellations, further steps may be necessary in accordance with current guideline recommendations.

Diagnostics to rule out hepatitis C requires sensibly coordinated steps[8]. HCV screening is based on the determination of anti-HCV antibodies. In certain case constellations, it may be necessary to verify the positive anti-HCV antibody findings in parallel or subsequently by HCV-RNA detection to confirm the diagnosis of an HCV infection.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Myeloablative conditioning with busulfan							
- Adults (3.2 mg/kg = 248.6 mg)	8 x 60 mg CIS	€ 1274.37	€ 1.77	€ 59.94	€ 1212.66	4	€ 3,637.98
- 12-year-olds (3.2 mg/kg = 150.7 mg)	8 x 60 mg CIS	€ 1274.37	€ 1.77	€ 59.94	€ 1212.66	4	€ 2,425.32
HBV screening							
HBV test Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.06	1.0	€ 5.06
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.43	1.0	€ 5.43
HCV screening							
Hepatitis C HCV antibody status	-	-	-	-	€ 9.02	1.0	€ 9.02

[5] Federal Statistical Office, Wiesbaden 2021: http://www.gbe-bund.de/
[6] Federal Statistical Office, Wiesbaden 2017: http://www.gbe-bund.de/
[7] S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011 https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf
[8] S3 guideline on prevention, diagnosis and therapy of hepatitis C virus (HCV) infection; AWMF registry no.: 021/012 https://register.awmf.org/assets/guidelines/021-012l_S3_Hepatitis-C-Virus_HCV-Infektion_2018-07.pdf

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
(GOP 32618)							
HIV screening							
HIV HIV-1 and HIV-2 antibody status (GOP: 32575)	-	-	-	-	€ 4.09	1.0	€ 4.09
Abbreviations: CIS = concentrate for the preparation of an infusion solution							

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active

ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be

attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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.

Justification for the findings on designation in the present resolution:

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

References:

Product information for exagamglogene autotemcel (Casgevy); Casgevy 4 – 13 × 10^6 cells/ml infusion dispersion; last revised: February 2025

2.6 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 exagamglogene autotemcel is a medicinal product placed on the market from 1 January 2025. In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

According to Section 35a, paragraph 1, sentence 3, no. 7 SGB V, the calculation is based on all studies conducted or commissioned by the pharmaceutical company, which they must submit to the G-BA as part of the benefit assessment dossier in the therapeutic indication to be assessed. The approval studies include all studies that were submitted to the regulatory authority in the authorisation dossier for the assessment of the clinical efficacy and safety of the medicinal product in the therapeutic indication to be assessed (see Section 4, paragraph 6, sentences 1 and 2 AM-NutzenV in conjunction with Chapter 5 Section 9, paragraph 4, sentences 1 and 2 VerfO).

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.

Section 2.7.4 of the Common Technical Document (CTD) does not clearly demarcate the studies submitted for the respective therapeutic indication. In the CLIMB-TDT-111 study, the percentage of study participants was 30.4%. Taking into account the additional CLIMB-SCD-121 study, there is a change in the percentage of study participants, which remains above 5%.

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.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 14 January 2025, the pharmaceutical company submitted a dossier for the benefit assessment of exagamglogene autotemcel to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 April 2025 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 6 May 2025.

The oral hearing was held on 26 May 2025.

An amendment to the benefit assessment with a supplementary assessment was submitted on 13 June 2025.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 24 June 2025, and the draft resolution was approved.

At their session on 3 July 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	8 April 2025	Information of the benefit assessment of the G-BA
Working group Section 35a	13 May 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	26 May 2025	Conduct of the oral hearing
Working group Section 35a	3 June 2025; 17 June 2025	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	24 June 2025	Concluding discussion of the draft resolution
Plenum	3 July 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 3 July 2025

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

Prof. Hecken