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To the Minister of Health, Welfare and Sport  
P.O. Box 20350  
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2025017091

Date 31 July 2025  
Re: Package advice for lock procedure medicinal product exagamglogene autotemcel (Casgevy®) for  $\beta$ -thalassemia

**National Health Care Institute**

Research, Development and Medicinal Products  
Medicinal Products Team

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**Contact**

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**Our reference**

2025017091

Dear Ms Jansen,

The National Health Care Institute advises you on the assessment of exagamglogene autotemcel (exa-cel; Casgevy®) for the treatment of transfusion-dependent  $\beta$ -thalassemia. This advice was prompted by the placement of exa-cel in the lock procedure for expensive medicinal products.

The National Health Care Institute advises you to include exa-cel for transfusion-dependent  $\beta$ -thalassemia in the basic healthcare package, provided that the net price is reduced by at least 43% after successful price negotiations.

$\beta$ -thalassemia is an inherited form of anaemia. There are various forms of  $\beta$ -thalassemia, from mild to severe. In severe  $\beta$ -thalassemia, patients are permanently dependent on blood transfusions that require hospital visits every 3 to 4 weeks. This is called transfusion-dependent  $\beta$ -thalassemia. In addition to anaemia, serious complications can occur. More than half of these patients die before the age of 50 years. There are approximately 350 patients in the Netherlands with  $\beta$ -thalassemia.  $\beta$ -thalassemia is included in the Guthrie test (heel prick) screening.

Children with transfusion-dependent  $\beta$ -thalassemia receive stem cells from a donor when available. This is called an allogeneic stem cell transplant. Adults with transfusion-dependent  $\beta$ -thalassemia are treated with chronic blood transfusions and iron chelation therapy to control iron overload. Luspatercept is a medicinal product that can be added to treatment to reduce the need for blood transfusion. However, due to limited effectiveness and side effects such as bone pain, luspatercept is used only to a limited extent.

Exa-cel is an innovative, one-time treatment of own stem cells, called an autologous stem-cell transplant, using so-called *CRISPR/Cas9* technology to genetically modify the stem cells.

### Registered indication

Exa-cel is indicated for the treatment of transfusion-dependent  $\beta$ -thalassaemia in patients aged 12 years and older for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen HLA-matched, related haematopoietic stem cell donor is not available.

Exa-cel is also registered for certain patients with sickle cell disease. For this, the assessment by the National Health Care Institute is still ongoing.

### Claim by the marketing authorisation holder

For the indication discussed here, exa-cel has added value over the standard treatment with lifetime blood transfusions, iron chelation therapy, and possibly luspatercept.

### **Package advice**

The National Health Care Institute advises you to include exa-cel for the above indication in the basic healthcare package, provided that, after successful price negotiations, the price can be reduced by at least 43% and agreements for appropriate use are made. The National Health Care Institute has established that exa-cel meets the legal criterion of 'established medical science and medical practice' for said indication and that it offers an added value compared to standard treatment with lifelong blood transfusions, iron chelation therapy and possibly luspatercept. However, based on the available data, the cost-effectiveness is unfavourable.

The price negotiations should include a discount of more than 43% due to the very high macro-costs when all 69 patients are treated with exa-cel. The total expenditure for exa-cel is likely to increase further due to the recent indication expansion to include patients with sickle cell disease, which is currently being assessed by the National Health Care Institute. Due to uncertainty about the continued effect of exa-cel, a reassessment by the National Health Care Institute could be requested prior to a re-negotiation of the price if more long-term data become available.

We explain the preparation of this package advice below.

### General

At your request, the National Health Care Institute assesses whether care should be part of the standard health insurance package from the perspective of the health insurance package paid from joint premiums.

The National Health Care Institute makes its assessments on the basis of four

**National Health Care  
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Research, Development and  
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**Date**  
31 July 2025

**Our reference**  
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package criteria<sup>1</sup>: effectiveness<sup>2</sup>, cost-effectiveness<sup>3</sup>, necessity<sup>4</sup> and feasibility<sup>5</sup>. The Scientific Advisory Board (WAR) advises the National Health Care Institute on the (scientific) basis and the conclusion of the assessment. If there are risks regarding the accessibility and affordability, the assessment of the package criterion of effectiveness (established medical science and medical practice) will be placed in the wider social context of the four package criteria. The Insured Package Advisory Committee (hereinafter also "ACP") advises the Executive Board of the National Health Care Institute in this regard. This social weighting results in the package advice. Stakeholders are consulted during the process.

**National Health Care Institute**  
Research, Development and Medicinal Products  
Medicinal Products Team

**Date**  
31 July 2025

**Our reference**  
2025017091

### Comprehensive weighting of package criteria

#### *Effectiveness*

##### *Established medical science and medical practice*

The single-arm CLIMB-THAL-111 study investigated exa-cel in patients with transfusion-dependent  $\beta$ -thalassemia. The study showed that 93% of patients treated no longer depended on blood transfusions for at least 12 months. It is unknown whether transfusion independence lasts for life, but so far, there are no signs that patients needed blood transfusions again. It also improved the quality of life of patients. The treatment course of exa-cel lasts several months and is intensive, but is comparable to that of allogeneic stem cell transplantation.

The National Health Care Institute, advised by the Scientific Advisory Board (WAR), has concluded that exa-cel has added value compared to standard blood transfusions, iron chelation therapy and possibly luspatercept treatment for the indication mentioned here.

#### *Cost-effectiveness*

The National Health Care Institute concludes that the model structure submitted by the marketing authorisation holder is sufficient for determining cost-effectiveness, but that the base-case analysis provided is unrealistic. In the opinion of the National Health Care Institute, other assumptions should be taken as a basis for estimating the effects and costs of exa-cel. These include assumptions about patient age, the effect on normalisation of iron levels, utilities, productivity costs, and informal care costs. The cost-effectiveness estimate calculated by the National Health Care Institute exceeds the reference value considered relevant for this condition, and therefore, exa-cel is not a cost-effective intervention at the current price. The weighted ICER is €168,103 per QALY compared to the standard treatment. With a reference value of €50,000, the price of exa-cel would have to be reduced by 43% to be cost-effective.

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<sup>1</sup> Real-world package management 4 (2023). National Health Care Institute, Diemen. Via [www.zorginstituutnederland.nl](http://www.zorginstituutnederland.nl).

<sup>2</sup> Assessment of the established medical science and medical practice (2023). National Health Care Institute. Via [www.zorginstituutnederland.nl](http://www.zorginstituutnederland.nl).

<sup>3</sup> Healthcare cost-effectiveness report (2024) National Health Care Institute, Diemen. Via [www.zorginstituutnederland.nl](http://www.zorginstituutnederland.nl).

<sup>4</sup> Necessity is related to both the medical need due to the severity of a disease for the patient (burden of disease) and the need to insure something. See the report on real-world package management 4 (2023).

<sup>5</sup> The package criterion of feasibility deals with whether it is feasible or sustainable to include a specific form of care in the basic healthcare package. It is therefore mainly a test of a number of implementation aspects such as the healthcare organisation, support, ethical and legal aspects, budget impact and so on. See the report on real-world package management 4 (2023).

### *Feasibility*

Currently, due to limited hospital capacity, it is not possible to treat all eligible patients with exa-cel immediately. Only 6 patients in the first year and 12 patients in the following years are expected to be treated with exa-cel. In addition, exa-cel is also currently being assessed by the National Health Care Institute for reimbursement for patients with sickle cell disease. If exa-cel also becomes available for this indication, the limited capacity will have to be divided between patients with transfusion-dependent  $\beta$ -thalassemia and sickle cell disease.

**National Health Care Institute**  
Research, Development and Medicinal Products  
Medicinal Products Team

**Date**  
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### *Budget impact analysis*

The National Health Care Institute estimates that, due to the stated capacity limitations, 12 patients per year will be treated with exa-cel for the indication mentioned in year 3 after inclusion in the package. The total cost per patient per year amounts to €1,909,500. This results in possible macro costs of €23 million in the third year. When substitution of iron chelation therapy and luspatercept is also taken into account, the budget impact will come to €22.5 million in year 3. Substitution of costs for blood transfusions has not been taken into account, as this does not involve costs for medicinal products. The costs of blood transfusions range from €9,876 to €16,840 per patient per year, depending on the source used. If all 69 patients are to be treated with exa-cel, the macro costs are €131 million.

### **Social appraisal**

The social appraisal shows that it is important that exa-cel for the treatment of transfusion-dependent  $\beta$ -thalassemia becomes available in the short term, but only at a socially acceptable price. Because of the high cost of exa-cel, price negotiations must take place. In addition, arrangements for appropriate use of exa-cel should be made determining the role of centres of expertise and the establishment of a national, multidisciplinary indication commission.

### **Appropriate use**

The National Health Care Institute acknowledges the importance of establishing arrangements for the appropriate use of exa-cel. Because of the rare nature of the disease, centralisation of care in centres of expertise is crucial. In addition, in order to determine which individual patients can start treatment, the National Health Care Institute recommends that, given the limited treatment capacity, an indication commission is created. The National Health Care Institute will contact the professional association, patient association and health insurers to provide a follow-up.

Should you need any further information, please do not hesitate to contact us. The assessment reports have been added as appendices (pharmacotherapeutic report, budget impact analysis, pharmaco-economic report).

Yours sincerely,

M.J. Janssen  
*Chairperson of the Executive Board*