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# 5.85.057

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**Last Review Date:** March 7, 2025

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## Casgevvy

### Description

#### Casgevvy (exagamglogene autotemcel)

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##### Background

Casgevvy (exagamglogene autotemcel) is a cellular gene therapy consisting of autologous CD34<sup>+</sup> hematopoietic stem cells (HSC) edited by CRISPR/Cas9-technology at the erythroid specific enhancer region of the *BCL11A* gene to reduce BCL11A expression in erythroid lineage cells, leading to increased fetal hemoglobin (HbF) protein production. Casgevvy is prepared from the patient's own HSCs, which are obtained via apheresis procedure(s). The autologous cells are enriched for CD34<sup>+</sup> cells, and then genome edited *ex vivo* by introducing the CRISPR/Cas9 ribonucleoprotein (RNP) complex by electroporation. The guide RNA included in the RNP complex enables CRISPR/Cas9 to make a precise DNA double-strand break at a critical transcription factor binding site (GATA1) in the erythroid specific enhancer region of the *BCL11A* gene. As a result of the editing, GATA1 binding is disrupted and BCL11A expression is reduced. This reduction conversely results in an increase in gamma-globin expression and downstream fetal hemoglobin formation (1).

After Casgevvy infusion, the edited CD34<sup>+</sup> cells engraft in the bone marrow and differentiate to erythroid lineage cells with reduced BCL11A expression. Reduced BCL11A expression results in an increase in  $\gamma$ -globin expression and HbF protein production in erythroid cells. In patients with severe sickle cell disease, HbF expression reduces intracellular hemoglobin S (HbS) concentration, preventing the red blood cells from sickling and addressing the underlying cause of disease, thereby eliminating vaso-occlusive crises (VOCs). In patients with transfusion-dependent  $\beta$ -thalassemia,  $\gamma$ -globin production improves the  $\alpha$ -globin to non- $\alpha$ -globin imbalance thereby reducing ineffective erythropoiesis and hemolysis and increasing total hemoglobin

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levels, addressing the underlying cause of disease, and eliminating the dependence on regular red blood cell (RBC) transfusions (1).

### Regulatory Status

FDA-approved indication: Casgevy is an autologous genome edited hematopoietic stem cell-based gene therapy indicated for the treatment of patients aged 12 years and older with (1):

- Sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs).
- Transfusion-dependent  $\beta$ -thalassemia (TDT).

Casgevy has warnings for neutrophil engraftment failure, delayed platelet engraftment, hypersensitivity reactions and off-target genome editing risk. The patient's absolute neutrophil count and platelet counts should be monitored. During and after infusion, the patient should be monitored for hypersensitivity reactions. Casgevy carries a risk of potential off-target genome editing due to genetic variants (1).

The safety and effectiveness of Casgevy in pediatric patients less than 12 years of age have not been established (1).

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### Related policies

Lyfgenia

#### [Policy](#)

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Casgevy may be considered **medically necessary** if the conditions indicated below are met.

Casgevy may be considered **investigational** for all other indications.

### Prior-Approval Requirements

**Age** 12 years of age or older

#### Diagnoses

Patient must have **ONE** of the following:

1. Heterozygous or homozygous sickle cell disease (SCD)

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- a. Diagnosis confirmed by genetic testing
  - b. Documented history of **ONE** of the following clinical signs or symptoms in the last 12 months:
    - i. Acute pain event requiring a visit to a medical facility and administration of pain medications (e.g., opioids (IV or oral), or intravenous non-steroidal anti-inflammatory drugs), hydration therapy, or red blood cell transfusion
    - ii. Acute chest syndrome
    - iii. Acute hepatic sequestration
    - iv. Acute splenic sequestration
    - v. Priapism lasting > 2 hours and requiring a visit to a medical facility
2. Transfusion-dependent  $\beta$ -thalassemia (TDT)
- a. Beta-thalassemia diagnosis has been confirmed by globin gene testing
  - b. Patient requires regular peripheral blood transfusions to maintain target hemoglobin levels
  - c. Patient has **ONE** of the following:
    - i. Documented history of receiving transfusions of  $\geq 100$  mL per kilogram of body weight of packed red cells per year
    - ii. Disease had been managed under standard thalassemia guidelines with  $\geq 8$  transfusions per year in the previous 2 years
  - d. No evidence of severe iron overload (e.g., T2\*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec)
- AND ALL** of the following for **ALL** diagnoses:
- a. Patient meets the institutional requirements for a stem cell transplant procedure including **ALL** of the following:
    - i. Adequate Karnofsky performance status or Lansky performance status
    - ii. Absence of advanced liver disease
    - iii. Adequate estimated glomerular filtration rate (eGFR)
    - iv. Adequate diffusing capacity of the lungs for carbon monoxide (DLCO)
    - v. Adequate left ventricular ejection fraction (LVEF)
    - vi. Absence of clinically significant active infection(s)
  - b. **NO** prior gene therapy or allogenic hematopoietic stem cell transplant

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## Prior – Approval *Renewal* Requirements

None

### Policy Guidelines

## Pre - PA Allowance

None

## Prior - Approval Limits

**Quantity** One infusion (only one PA approval for one infusion per lifetime)

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## Prior – Approval *Renewal* Limits

None

### Rationale

#### Summary

Casgevy is an autologous genome edited hematopoietic stem cell-based gene therapy indicated for the treatment of sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs) and for the treatment of transfusion-dependent  $\beta$ -thalassemia (TDT). The safety and effectiveness of Casgevy in pediatric patients less than 12 years of age have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Casgevy while maintaining optimal therapeutic outcomes.

#### References

1. Casgevy [Package Insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; January 2024.

### Policy History

Date	Action
April 2024	Addition to PA
June 2024	Annual review
March 2025	Annual review

### Keywords

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**This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 7, 2025 and is effective on April 1, 2025.**