EXPRESS SCRIPTS®

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Gene Therapy – Casgevy UM Medical Policy
- Casgevy™ (exagamglogene autotemcel intravenous infusion – Vertex/CRISPR Therapeutics)

REVIEW DATE: 09/30/2026

OVERVIEW

Casgevy, an autologous hematopoietic stem cell (HSC)-based gene therapy, is indicated for the following uses:[1]
- **Sickle cell disease** in patients ≥ 2 years of age with recurrent vaso-occlusive crises (VOCs).
- **Transfusion-dependent beta-thalassemia** (TDT) in patients ≥ 2 years of age.

The prescribing information notes that it is recommended that patients weigh ≥ 12 kg prior to start of mobilization since patients below this weight may experience difficulty in achieving the minimum target cell dose.[1]

Casgevy is given one-time (per lifetime) as a single dose, which contains a minimum of 3 x 10^6 cluster of differentiation 34+ (CD34+) cells/kg of body weight.[1] Casgevy is given as an intravenous (IV) infusion. The manufacturing time (which includes quality control) for Casgevy can take up to 6 months. However, the entire process can take 8 months or longer as patients need to undergo mobilization and apheresis procedures and myeloablative conditioning prior to Casgevy infusion.

Casgevy is prepared from the patient's own hematopoietic stem cells (HSCs).[1,2] The CD34+ cells collected from the patient are modified *ex vivo* by highly specific clustered, regularly interspaced, short palindromic repeats (CRISPR) and CRISPR-associated protein 9 nucleases (CRISPR/Cas9)-mediated gene editing. CRISPR/Cas9 specifically edits the B-cell lymphoma/leukemia 11A (*BCL11A*) gene which results in increased fetal hemoglobin (HbF) production and an increase in γ-globin expression. In patients with sickle cell disease, increased HbF levels (≥ 20%) are protective against disease complications, including prevention of VOCs.[2] In patients with TDT, γ-globin production reduces ineffective erythropoiesis and hemolysis and increases total hemoglobin (Hb) levels, which eliminates the dependence on red blood cell (RBC) transfusions.[1,2]

Disease Overview

Sickle Cell Disease

Sickle cell disease is a group of inherited RBC disorders characterized by the presence of a Hb subunit beta gene variant.[3-6] Healthy RBCs are round and contain Hb. In contrast, in a patient with sickle cell disease, RBCs are sickle-shaped and die early, resulting in a constant shortage of RBCs. Furthermore, the sickle-shaped RBCs aggregate in the bloodstream, causing vaso-occlusion, which deprive downstream tissues of nutrients and oxygen, resulting in tissue ischemia, organ damage, and hemolysis (which leads to anemia). In the US, approximately 100,000 persons have the condition, and it is estimated 20,000 patients have severe sickle cell disease.[2,3]

Patients with severe sickle cell disease have one of the following genotypes: β^S/β^S, β^S/β^0, β^S/β^+.[2-5] These patients have recurrent VOCs/vaso-occlusive events, while receiving appropriate supportive care (e.g., pain management, hydroxyurea). Management of sickle cell disease focuses on preventing and treating pain

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episodes and other complications; symptomatic treatment includes use of analgesics, fluids (hydration), oxygen supplementation, and blood transfusion.[3,5,6] Allogeneic hematopoietic stem cell transplantation (HSCT), a potentially curative therapy, requires a stem cell donor, typically a human leukocyte antigen (HLA)-matched donor; less than 20% of patients with sickle cell disease have a suitable donor.[2] Pharmacologic treatments for sickle cell disease include Adakveo® (crizanlizumab-tmca IV infusion), L-glutamine oral powder (Endari®, generic), hydroxyurea, and Oxbryta® (voxelotor tablets and tablets for oral suspension) [no longer available].[7-11]

Transfusion-Dependent Beta-Thalassemia (TDT)
The condition of beta-thalassemia is a group of recessively inherited blood disorders caused by beta-globin gene variants that either reflect a reduced (β^+) or relative lack (β^0) of production of functional beta-globin.[12] The attenuated or lack of Hb results in chronic anemia of varying degrees of severity and insufficient delivery of oxygen to the body. Those with severe anemia may require lifelong RBC transfusions and regular iron chelation to prevent iron overload. The extremely low Hb levels can lead to many types of symptoms and health-related issues (e.g., dizziness, weakness, fatigue, increased cardiac effort, tachycardia, poor growth) or ineffective erythropoiesis (e.g., bone changes, massive splenomegaly). An estimated 3,000 persons in the US have beta-thalassemia and slightly less than one-half of the patients are dependent on RBC transfusions.

Clinical Efficacy

Sickle Cell Disease
Casgevy was evaluated in two multicenter, open-label, single-arm studies; Study 1 included patients ≥ 12 years of age (n = 44) and Study 2 included patients 5 years to < 12 years of age and weighed ≥ 12 kg (n = 11).[1,2,13,18] Note that Casgevy has not been studied in patients < 5 years of age in clinical studies. Use of Casgevy in pediatric patients 2 years to < 5 years of age with sickle cell disease is supported by extrapolation of data from two adequate and well-controlled studies (Study 1 and Study 2).[1]

Enrolled patients had documented β^S/β^S, β^S/β^0, or β^S/β^+ genotype and a history of at least two protocol-defined severe VOC events during each of the 2 years prior to screening.[1] Severe VOC is defined as an occurrence of at least one of the following events: acute pain (including dactylitis for Study 2) requiring a visit to a medical facility and administration of pain medications or RBC transfusions; acute chest syndrome; priapism lasting > 2 hours and requiring a visit to a medical facility; and splenic sequestration. Key exclusions included patients with an available 10/10 HLA-matched related HSC donor, advanced liver disease, or history of untreated Moyamoya disease or Moyamoya disease at risk of bleeding. Patients were followed for 24 months after Casgevy infusion and were eligible to enroll in the ongoing, long-term follow-up for a total of 15 years after Casgevy infusion.

The primary efficacy outcome was the proportion of patients who did not experience any protocol-defined severe VOCs for ≥ 12 consecutive months within the first 24 months after Casgevy infusion (VF12).[1] The key secondary efficacy outcome was the proportion of patients who did not require hospitalization due to severe VOCs for ≥ 12 consecutive months within the 24-month evaluation period (HF12). Evaluation of VF12 and HF12 began 60 days after the last RBC transfusion for post-transplant support or sickle cell disease management.

Study 1 (≥ 12 years of age). In total, 44 patients received a Casgevy infusion and 30 patients had ≥ 16 months of follow-up after Casgevy infusion (primary efficacy population).[1] One patient who did not have 16 months of follow-up was determined to be a non-responder and was included in the efficacy analysis. In the subset of 31 evaluable patients (24 adults, 7 adolescents), the median annualized rate of severe VOCs and hospitalizations due to severe VOCs in the 2 years prior to enrollment were 3.5 and 2.0 events per year,

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respectively. *Results*. The VF12 response was achieved in 93.5% (98% one sided confidence interval [CI]: 77.9%, 100%]) of patients (n = 29/31); median duration of VOC-free period was 22.2 months. Thirty of these patients were evaluable for the HF12 response and all 30 (100% [98% one sided CI: 87.8%, 100%]) achieved HF12.

Study 2 (5 years to < 12 years of age). In total, 11 patients received a Casgevy infusion and 8 patients had ≥ 16 months of follow-up after Casgevy infusion (primary efficacy population).[1] All 8 patients (100%) achieved VF12; median duration of VOC-free period was 17.5 months. In addition, all eight patients achieved HF12.

Transfusion-Dependent Beta-Thalassemia (TDT)
Casgevy was evaluated in two multicenter, open-label, single-arm studies; Study 3 included patients ≥ 12 years of age (n = 52) and Study 4 included patients 5 years to < 12 years of age and weighed ≥ 12 kg (n = 15).[1,14,18] Note that Casgevy has not been studied in patients < 5 years of age in clinical studies.[1] Use of Casgevy in pediatric patients 2 years to < 5 years of age with TDT is supported by extrapolation of data from two adequate and well-controlled studies (Study 3 and Study 4).

Enrolled patients had β^0/β^0-like or non-β^0/β^0-like genotypes and a history of requiring ≥ 100 mL/kg/year or ≥ 10 units/year of RBC transfusions in the 2 years prior to enrollment.[1] In addition, in patients 5 years to < 12 years of age who started transfusion therapy < 24 months before study consent, a history of requiring packed RBC transfusions at least every 3 to 4 weeks for ≥ 6 months was required.[18] Key exclusions included patients with an available 10/10 HLA-matched related HSC donor, severely elevated iron in the heart (i.e., patients with cardiac T2* < 10 msec by magnetic resonance imaging [MRI] or left ventricular ejection fraction < 45% by echocardiogram), or advanced liver disease.[1] Patients were followed for 24 months after Casgevy infusion and were eligible to enroll in the ongoing, long-term follow-up for a total of 15 years after Casgevy infusion.

The primary efficacy outcome was the proportion of patients who achieved transfusion independence for 12 consecutive months, defined as maintaining weighted average hemoglobin (Hb) level ≥ 9 g/d without RBC transfusions for at least 12 consecutive months any time within the first 24 months after Casgevy infusion.[1] Evaluation began 60 days after the last RBC transfusion for post-transplant support or TDT management.

Study 3 (≥ 12 years of age). In total, 52 patients received a Casgevy infusion and 35 patients had ≥ 16 months of follow-up after Casgevy infusion (primary efficacy population).[1] In the subset of 35 evaluable patients (24 adults, 11 adolescents), the median annualized transfusion volume and number of transfusion episodes were 205 mL/kg and 17, respectively at baseline. *Results*. In total, 91.4% (98.3% one sided CI: 75.7%, 100%) of patients (n = 32/35) achieved transfusion independence for 12 consecutive months. The median duration of transfusion independence was 20.8 months and the normal mean weighted average total Hb level was 13.1 g/dL. The three patients who did not achieve transfusion independence had reductions in annualized RBC transfusion volume requirements and reductions in annualized transfusion frequency compared with baseline.

Study 4 (5 years to < 12 years of age). In total, 15 patients received a Casgevy infusion and 8 patients had ≥ 16 months of follow-up after Casgevy infusion (primary efficacy population).[1] One additional patient who died of vaso-occlusive disease following treatment was included in the efficacy analysis. Of the 9 evaluable patients, the median annualized transfusion volume and number of transfusion episodes were 232 mL/kg and 14, respectively at baseline. *Results*. In total 89% of patients (n = 8/9) achieved transfusion independence for 12 consecutive months. The median duration of transfusion independence was 20.1

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months and the normal mean weighted average total Hb level was 11.7 g/dL. Note that in the group of nine patients included in the efficacy analysis, one patient died prior to 16 months.

Guidelines

Sickle Cell Disease

Sickle cell disease guidelines have not incorporated gene therapies following their FDA approval. The American Society of Hematology (ASH) released evidence-based recommendations for stem cell transplantation for patients with sickle cell disease in 2021.[15] ASH notes that it is unclear how gene therapies will affect sickle cell disease outcomes, including organ complications and if broader access to curative therapy will alter the trajectory of sickle cell disease outcomes. ASH notes that while success rates after allogeneic HSCT are increasing, survival rates in patients receiving disease-modifying medications (e.g., hydroxyurea, L-glutamine, Adakveo, Oxbryta [no longer available]) and supportive care are also improving. More than 90% of patients who have undergone HSCT (predominantly using HLA-identical family donors) have been cured of sickle cell disease, as reported in short-term follow-up studies. Allogeneic HSCT is an established therapeutic option for patients with sickle cell disease with a clinical indication and an HLA-identical family donor. However, for the majority of patients, there are no suitable donors.

Transfusion-Dependent Beta-Thalassemia (TDT)

The Thalassemia International Federation (TIF) guidelines for the management of TDT (2025) address the use of gene therapies, including Casgevy.[16] TIF notes that allogeneic hematopoietic cell transplantation (HCT) has been the first therapeutic option for curing TDT. Substantial improvement in patient outcomes has been observed with HCT over recent years due to multiple factors, including improved conditioning regimens, improved prevention of graft-versus-host disease (GVHD), more effective antibacterial, antiviral, and antifungal treatment, and significant improvement in the medical care of TDT. However, more than 60% of patients do not have a suitable sibling donor; although HCT from a matched unrelated donor can also lead to successful results. TIF notes that HCT should be offered to patients with TDT at an early age, before complications due to iron overload develop. Gene therapy (including Casgevy) may redefine the role of allogeneic transplantation. TIF notes that for patients ≥ 14 years of age who do not have an HLA-identical family donor, gene therapy is an optimal therapeutic option to allogeneic HCT. The main advantages of gene therapy are that a donor is not needed and there are no limitations or risks associated with donor availability/compatibility; absence/reduction of immune-mediated complications (e.g., no risk of GVHD or graft rejection); and lower toxicity (e.g., from the conditioning regimen). These advantages may allow more patients to access a curative treatment. However, there are potential risks with gene therapy, including insertional mutagenesis/insertional oncogenesis and DNA alterations (associated with genome editing). TIF notes that the risk of translocations with CRISPR-Cas9 editing is mitigated by the high precision of genome editing and the minimization of off-target editing events. In addition, TIF notes that to date, there have been no cases of insertional oncogenesis reported in patients with TDT who were treated with Zynteglo™ (betibeglogene autotemcel IV infusion), another gene therapy also approved for the treatment of TDT.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Casgevy. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Because of the specialized skills required for evaluation and diagnosis of patients treated with Casgevy as well as the specialized training required for administration of Casgevy, approval requires Casgevy to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. The approval duration is 1 year to allow for an adequate timeframe to prepare and administer one

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dose of therapy. If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. For the dosing criteria, verification of the appropriate weight-based dosing is required by a Medical Director as noted by **[verification required]**. In the criteria for Casgevy, as appropriate, the symbol (†) is noted next to the specified gender. In this context, the specified gender is defined as follows: females/males are defined as individuals with the biological traits of a woman/man, regardless of the individual's gender identity or gender expression.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with EviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@EviCore.com prior to completing the review.

Documentation: Documentation is required for use of Casgevy as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information. All documentation must include patient-specific identifying information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Casgevy is recommended in those who meet ONE of the following criteria:

FDA-Approved Indications

1. **Sickle Cell Disease.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O):
   - **A)** Patient is ≥ 2 years of age and weighs ≥ 12 kg; AND
   - **B)** Patient has not received a gene therapy for sickle cell disease in the past **[verification in claims history required]**; AND
     Note: If no claim for Casgevy or Lyfgenia (lovotibeglogene autotemcel intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Casgevy or Lyfgenia.
   - **C)** According to the prescribing physician, a hematopoietic stem cell transplantation is appropriate for the patient; AND
   - **D)** Patient meets ONE of the following (i or ii):
     - **i.** Patient does not have a Human Leukocyte Antigen (HLA)-matched related donor; OR
     - **ii.** Patient has an HLA-matched related donor, but the individual is not able or is not willing to donate; AND
   - **E)** Genetic testing **[documentation required]** indicates the patient has ONE of the following sickle cell disease genotypes (i, ii, or iii):
     - **i.** β^S/β^S genotype; OR
     - **ii.** β^S/β^0 genotype; OR
     - **iii.** β^S/β^+ genotype; AND
     Note: Other genotypes will be reviewed by the Medical Director on a case-by-case basis.
   - **F)** Patient has tried at least ONE pharmacologic treatment for sickle cell disease **[documentation required]**; AND

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Note: Examples of pharmacologic treatment for sickle cell disease include hydroxyurea, L-glutamine, Adakveo (crizanlizumab-tmca intravenous infusion), and Oxbryta (voxelotor tablets and tablets for oral suspension) [no longer available].

G) While receiving appropriate standard treatment for sickle cell disease, patient had at least four severe vaso-occlusive crises or events in the previous 2 years **[documentation required]**; AND
Note: Examples of severe vaso-occlusive crises or events include the following:
- An episode of dactylitis (in a patient < 5 years of age);
- An episode of acute pain that resulted in a visit to a medical facility which required administration of an intravenous opioid and/or intravenous nonsteroidal anti-inflammatory drug;
- Acute chest syndrome, which is defined by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms (e.g., chest pain, fever [> 101.3°F], tachypnea, wheezing or cough, or findings upon lung auscultation);
- Acute hepatic sequestration, which is defined by a sudden increase in liver size associated with pain in the right upper quadrant, abnormal results of liver function test not due to biliary tract disease, and the reduction of hemoglobin concentration by ≥ 2 g/dL below the baseline value;
- Acute splenic sequestration, which is defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in hemoglobin concentration of ≥ 2 g/dL below the baseline value;
- Acute priapism lasting > 2 hours and requiring a visit to a medical facility.

H) Patient does not have the following (i, ii, iii, iv, and v):
- **i.** Clinically significant and active bacterial, viral, fungal, or parasitic infection; AND
- **ii.** Advanced liver disease **[documentation required]**; AND
  Note: Examples of advanced liver disease include alanine transaminase > 3 times upper limit of normal; direct bilirubin value > 2.5 times upper limit of normal; baseline prothrombin time (international normalized ratio [INR]) > 1.5 times upper limit of normal; cirrhosis; bridging fibrosis; or active hepatitis.
- **iii.** Severe cerebral vasculopathy as defined by history of untreated Moyamoya disease or presence of Moyamoya disease that puts the patient at risk of bleeding, per the prescribing physician; AND
- **iv.** History of abnormal transcranial doppler (if the patient is < 18 years of age); AND
- **v.** Prior or current malignancy, myeloproliferative disorder, or significant immunodeficiency disorder; AND

I) According to the prescribing physician, patient will have been discontinued from the following medications (for the duration noted) [i and ii]:
- **i.** Disease-modifying therapies for sickle cell disease for at least 2 months before the planned start of mobilization and conditioning; AND
  Note: Examples of disease-modifying therapies for sickle cell disease include hydroxyurea, Adakveo, L-glutamine, and Oxbryta (no longer available).
- **ii.** Iron chelation therapy for at least 7 days prior to myeloablative conditioning; AND
  Note: Examples of iron chelators used for this condition include deferoxamine injection, deferiprone tablets or solution, and deferasirox tablets.

J) According to the prescribing physician, patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient will undergo mobilization, apheresis, and myeloablative conditioning; AND
- **ii.** A hematopoietic stem cell mobilizer will be utilized for mobilization; AND
  Note: Mozobil (plerixafor subcutaneous injection) is an example of a hematopoietic stem cell mobilizer.
- **iii.** Busulfan will be used for myeloablative conditioning; AND
  Note: Pharmacokinetically guided busulfan dosing is recommended for myeloablative conditioning.

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iv. Patient meets BOTH of the following (a and b):
- **a)** Sickle hemoglobin level goal is < 30% of total hemoglobin; AND
- **b)** Total hemoglobin level goal is ≤ 11 g/dL; AND

K) Patient screening is negative for ALL of the following (i, ii, iii, and iv):
- **i.** Human immunodeficiency virus-1 and -2 **[documentation required]**; AND
- **ii.** Hepatitis B virus **[documentation required]**; AND
  Note: A patient who has been vaccinated against hepatitis B virus (HBV) [HBV surface antibody-positive] who is negative for other markers of prior HBV infection (e.g., negative for HBV core antibody) is eligible; a patient with past exposure to HBV is also eligible as long as patient is negative for HBV DNA.
- **iii.** Hepatitis C virus **[documentation required]**; AND
- **iv.** Human T-lymphotropic virus-1 and -2 **[documentation required]**; AND

L) Patient meets ONE of the following (i or ii):
- **i.** According to the prescribing physician, the patient is not of reproductive potential; OR
- **ii.** According to the prescribing physician, the patient is of reproductive potential and meets ONE of the following (a or b):
  - **a)** A female† of reproductive potential meets BOTH of the following ([1] and [2]):
    - **(1)** A negative serum pregnancy test will be confirmed prior to the start of each mobilization cycle and re-confirmed prior to myeloablative conditioning; AND
    - **(2)** Patient will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Casgevy; OR
  - **b)** A male† of reproductive potential will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Casgevy; AND

M) The medication is prescribed by a hematologist or a stem cell transplant physician; AND

N) Current patient body weight has been obtained within 30 days **[documentation required]**; AND

O) If criteria A through N are met, approve one dose of Casgevy by intravenous infusion to provide a one-time (per lifetime) single dose, which contains a minimum of 3 x 10^6 CD34+ cells/kg of body weight **[verification required]**.
Note: A single dose of Casgevy is composed of one or more vial(s).

† Refer to the Policy Statement.

Dosing. The recommended dose of Casgevy is a one-time (per lifetime) single intravenous infusion of a minimum of 3 x 10^6 CD34+ cells per kg of body weight.

2. Transfusion-Dependent Beta-Thalassemia. Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, and Q):

A) Patient is ≥ 2 years of age and weighs ≥ 12 kg; AND

B) Patient has not received a gene therapy for beta-thalassemia in the past **[verification in claims history required]**; AND
Note: If no claim for Casgevy or Zynteglo (betibeglogene autotemcel intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Casgevy or Zynteglo.

C) According to the prescribing physician, a hematopoietic stem cell transplantation is appropriate for the patient; AND

D) Patient meets ONE of the following (i or ii):
- **i.** Patient does not have a Human Leukocyte Antigen (HLA)-matched related donor; OR
- **ii.** Patient has an HLA-matched related donor, but the individual is not able or is not willing to donate; AND

E) Patient has ONE of the following genotypes as confirmed by genetic testing (i or ii):

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i. Non-β^0/β^0 genotype **[documentation required]**; OR
Note: Examples include β^0/β^+, β^E/β^0, and β^+/β^+.
ii. β^0/β^0 genotype **[documentation required]**; AND
Note: Other examples include $\beta^0/\beta^{+(IVS\text{-}I\text{-}110)}$ and $\beta^{+(IVS\text{-}I\text{-}110)}/\beta^{+(IVS\text{-}I\text{-}110)}$.

F) Patient is transfusion-dependent, as defined by meeting ONE of the following (i or ii):
i. For patients 2 to 11 years of age, patient meets ONE of the following (a or b):
a) For patients who initiated transfusion therapy < 2 years ago, receipt of transfusions of packed red blood cells at least every 3 to 4 weeks for ≥ 6 months **[documentation required]**; OR
b) For patients who initiated transfusion therapy ≥ 2 years ago, patient meets ONE of the following ([1] or [2]):
(1) Receipt of transfusions of ≥ 100 mL of packed red blood cells per kg of body weight per year in the previous 2 years **[documentation required]**; OR
(2) Receipt of transfusions of ≥ 10 units of packed red blood cells per year in the previous 2 years **[documentation required]**; OR
ii. For patients ≥ 12 years of age, patient meets ONE of the following (a or b):
a) Receipt of transfusions of ≥ 100 mL of packed red blood cells per kg of body weight per year in the previous 2 years **[documentation required]**; OR
b) Receipt of transfusions of ≥ 10 units of packed red blood cells per year in the previous 2 years **[documentation required]**; AND

G) Patient meets BOTH of the following (i and ii):
i. Patient has been evaluated for the presence of severe iron overload **[documentation required]**; AND
ii. Patient does not have evidence of severe iron overload; AND
Note: Examples include abnormal myocardial iron results (a T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec); high liver iron concentration (≥ 15 mg/g unless a liver biopsy within the past 3 months showed no evidence of bridging or septal fibrosis or cirrhosis); liver biopsy results suggest abnormalities; or clinical evidence of organ damage (e.g., endocrine comorbidities).

H) Patient does not currently have an active bacterial, viral, fungal, or parasitic infection; AND

I) Patient does not have the following (i and ii):
i. Prior or current malignancy, myeloproliferative disorder, or significant immunodeficiency disorder; AND
Note: This does not include adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin.
ii. Advanced liver disease **[documentation required]**; AND
Note: Examples include alanine transaminase or aspartate transaminase greater than three times upper limit of normal, direct bilirubin value greater than three times upper limit of normal, active hepatitis, extensive bridging fibrosis, or cirrhosis.

J) According to the prescribing physician, patient will have been discontinued from iron chelation therapy for at least 7 days prior to myeloablative conditioning; AND
Note: Examples of iron chelators used for this condition include deferoxamine injection, deferiprone tablets or solution, and deferasirox tablets.

K) According to the prescribing physician, patient meets ALL of the following (i, ii, iii, and iv):
i. Patient will undergo mobilization, apheresis, and myeloablative conditioning; AND
ii. A granulocyte-colony stimulating factor product and a hematopoietic stem cell mobilizer will be utilized for mobilization; AND
Note: Filgrastim products are examples of a granulocyte-colony stimulating factor therapy and Mozobil (plerixafor subcutaneous injection) is an example of a hematopoietic stem cell mobilizer.

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iii. Busulfan will be used for myeloablative conditioning; AND
Note: Pharmacokinetically guided busulfan dosing is recommended for myeloablative conditioning.
iv. Total hemoglobin level goal is ≥ 11 g/dL; AND

L) Patient screening is negative for ALL of the following (i, ii, iii, and iv):
i. Human immunodeficiency virus-1 and -2 **[documentation required]**; AND
ii. Hepatitis B virus **[documentation required]**; AND
iii. Hepatitis C virus **[documentation required]**; AND
iv. Human T-lymphotropic virus-1 and -2 **[documentation required]**; AND

M) Patient meets ONE of the following (i or ii):
i. According to the prescribing physician, the patient is not of reproductive potential; OR
ii. According to the prescribing physician, the patient is of reproductive potential and meets ONE of the following (a or b):
a) A female† of reproductive potential meets BOTH of the following ([1] and [b]):
(1) A negative serum pregnancy test will be confirmed prior to the start of each mobilization cycle and re-confirmed prior to myeloablative conditioning; AND
(2) Patient will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Casgevy; OR
b) A male† of reproductive potential will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Casgevy; AND

N) Patient does not have any of the following (i and ii):
i. Associated alpha-thalassemia and more than one alpha deletion or alpha multiplication; AND
ii. Sickle cell beta-thalassemia variant; AND

O) The medication is prescribed by a hematologist or a stem cell transplant physician; AND

P) Current patient body weight has been obtained within 30 days **[documentation required]**; AND

Q) If criteria A through P are met, approve one dose of Casgevy by intravenous infusion to provide a one-time (per lifetime) single dose, which contains a minimum of 3 x 10^6 CD34+ cells/kg of body weight **[verification required]**.
Note: A single dose of Casgevy is composed of one or more vial(s).

† Refer to the Policy Statement.

Dosing. The recommended dose of Casgevy is a one-time (per lifetime) single intravenous infusion of a minimum of 3 x 10^6 CD34+ cells per kg of body weight.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Casgevy is not recommended in the following situations:

1. **Prior Hematopoietic Stem Cell Transplantation.**
Note: The prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.
Casgevy has not been studied in a patient who has received a prior allogeneic or autologous hematopoietic stem cell transplant.[1] Treatment with Casgevy is not recommended.

2. **Prior Receipt of Gene Therapy.** Casgevy has not been studied in a patient who has received prior gene therapy such as Lyfgenia® (lovotibeglogene autotemcel intravenous infusion) and Zynteglo™ (betibeglogene autotemcel intravenous infusion).[1] Treatment with Casgevy is not recommended.

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3. **Concurrent Use with Aqvesme™ (mitapivat tablets) or Reblozyl® (luspatercept-aamt subcutaneous injection)**. Patients who had previously received gene therapy were excluded from the Aqvesme pivotal study involving patients with TDT.[17] Reblozyl was not utilized with Casgevy in the pivotal trial assessing the efficacy of Casgevy in patients with transfusion-dependent beta-thalassemia.[1]

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Casgevy™ intravenous infusion [prescribing information]. Waltham, MA: Vertex; July 2026.
2. Vertex: Exagamglogene autotemcel (exa-cel) for the treatment of sickle cell disease in patients 12 years and older with recurrent vaso-occlusive crises. FDA Cellular, Tissue and Gene Therapies Advisory Committee. October 31, 2023.
3. Kavanagh PL, Fasipe TA, Wun T. Sickle cell disease: a review. *JAMA*. 2022;328(1):57-68.
4. Piel FB, Steinberg MH. Sickle cell disease. *N Engl J Med*. 2017;376:1561-1573.
5. Centers for Disease Control and Prevention – Sickle cell disease. Available at: https://www.cdc.gov/sickle-cell/. Accessed on September 1, 2026.
6. Patel ZV, Prajjwal P, Bethineedi LD, et al. New modalities and updates in the management of sickle cell disease: a systematic review. *J Blood Med*. 2024;15:435-447.
7. Adakveo® intravenous injection [prescribing information]. East Hanover, NJ: Novartis; June 2024.
8. Endari™ oral powder [prescribing information]. Torrance, CA: Emmaus Medical; June 2025.
9. Droxia® capsules [prescribing information]. Rahway, NJ: Waylis Therapeutics; June 2025.
10. Siklos® tablets [prescribing information]. Bryn Mawr, PA: Medunik; November 2023.
11. Oxbryta® tablets and tablets for oral suspension [prescribing information]. San Francisco, CA: Global Blood Therapeutics; August 2023.
12. Taher AT, Musallam KM, Cappellini MD, et al. β-thalassemias. *N Engl J Med*. 2021;384;727-743.
13. Frangoul H, Locatelli F, Sharma A, et al. Exagamglogene autotemcel for severe sickle cell disease. *N Engl J Med*. 2024;390:1649-1662.
14. Locatelli F, Lang P, Wall R, et al. Exagamglogene autotemcel for transfusion-dependent β-thalassemia. *N Engl J Med*. 2024;390:1663-1676.
15. Kanter J, Liem RI, Bernaudin F, et al. American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation. *Blood Adv*. 2021;5:3668-3689.
16. Taher AT, Farmakis D, Porter JB, Cappellini MD, Musallam KM, editors. Guidelines for the Management of Transfusion-Dependent β-Thalassaemia (TDT) [Internet]. 5th ed. Nicosia, Cyprus: Thalassaemia International Federation; 2025. PMID: 40367250.
17. Cappellini MD, Sheth S, Taher AT, et al. ENERGIZE-T: a global, Phase 3, double-blind, randomized, placebo-controlled study of mitapivat in adults with transfusion-dependent alpha- or beta-thalassemia (slides) Presented at: the 66th American Society of Hematology Annual Meeting and Exposition; San Diego, CA; December 7-10, 2024. Available at: https://www.agios.com/wp-content/uploads/2024/12/409_ASH24_Sun940amPT.pdf. Accessed on September 1, 2026.
18. Frangoul H, de la Fuente J, Chopra Y, et al. Exa-cel in children with transfusion-dpendent β-thalassemia or sickle cell disease. *N Engl J Med*. 2026 Jun 11. doi: 10.1056/NEJMoa2603387. Online ahead of print.

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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Sickle Cell Disease:** **1.** The word "cellular" was removed from the criterion regarding screening for certain viruses prior to collection of cells for manufacturing; the new criterion reads: Prior to collection of cells for manufacturing, screening is negative for ALL of the following. **2.** The criterion regarding females/males of reproductive potential was clarified that the criterion pertains to patients of reproductive potential. Previously, the criterion read: "According to the prescribing physician, patient meets ONE of the following"; revised criterion reads: "According to the prescribing physician, a patient of reproductive potential meets ONE of the following". **Transfusion-Dependent Beta-Thalassemia:** **1.** The word "cellular" was removed from the criterion regarding screening for certain viruses prior to collection of cells for manufacturing; the new criterion reads: Prior to collection of cells for manufacturing, screening is negative for ALL of the following. **2.** The criterion regarding females/males of reproductive potential was clarified that the criterion pertains to patients of reproductive potential. Previously, the criterion read: "According to the prescribing physician, patient meets ONE of the following"; revised criterion reads: "According to the prescribing physician, a patient of reproductive potential meets ONE of the following".	02/05/2025
Selected Revision	**Sickle Cell Disease:** The requirement that the patient had at least four severe vaso-occlusive crises or events in the previous 2 years was revised such that the definitions of severe vaso-occlusive crises or events are now listed as examples (as a Note) rather than as a specific list as previously in the criteria. The qualifier "Prior to collection of cells for manufacturing" was removed from the requirement regarding screening for certain viruses and the word "Patient" was added. The new criterion now reads: "Patient screening is negative for ALL of the following…". **Transfusion-Dependent Beta-Thalassemia:** The qualifier "Prior to collection of cells for manufacturing" was removed from the requirement regarding screening for certain viruses and the word "Patient" was added. The new criterion now reads: "Patient screening is negative for ALL of the following...".	04/23/2025
Annual Revision	**Sickle Cell Disease:** The dosing was clarified that the recommended dose is a minimum of 3 x 10^6 CD34+ cells per kg. Also, the qualifier regarding body weight "within the past 30 days" was removed. Previously, the dosing was: The recommended dose of Casgevy is a one-time (per lifetime) single intravenous infusion of 3 x 10^6 CD34+ cells per kg based on current body weight in kg (within the past 30 days). The new dosing reads: The recommended dose of Casgevy is a one-time (per lifetime) single intravenous infusion of a minimum of 3 x 10^6 CD34+ cells per kg of body weight. **Transfusion-Dependent Beta-Thalassemia:** The dosing was clarified that the recommended dose is a minimum of 3 x 10^6 CD34+ cells per kg. Also, the qualifier regarding body weight "within the past 30 days" was removed. Previously, the dosing was: The recommended dose of Casgevy is a one-time (per lifetime) single intravenous infusion of 3 x 10^6 CD34+ cells per kg based on current body weight in kg (within the past 30 days). The new dosing reads: The recommended dose of Casgevy is a one-time (per lifetime) single intravenous infusion of a minimum of 3 x 10^6 CD34+ cells per kg of body weight. **Conditions Not Recommended for Approval**, the condition "Concurrent Use with Reblozyl (luspatercept-aamt subcutaneous injection)" was revised to "Concurrent Use with Aqvesme (mitapivat tablets) or Reblozyl (luspatercept-aamt subcutaneous injection)".	02/11/2026

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HISTORY (CONTINUED)

Type of Revision	Summary of Changes	Review Date
Selected Revision	**Sickle Cell Disease:** The minimum age was changed to ≥ 2 years of age and a minimum weight (≥ 12 kg) was added. **Transfusion-Dependent Beta-Thalassemia:** The minimum age was changed to ≥ 2 years of age and a minimum weight (≥ 12 kg) was added. The requirement regarding definition of transfusion dependence was updated to include definitions for patients 2 to 11 years of age. It was clarified that the existing definitions pertain to patients ≥ 12 years of age.	07/15/2026
Early Annual Revision	**Sickle Cell Disease:** For following changes were made: 1. For the requirement regarding Human Leukocyte Antigen (HLA)-matched donor, the word "related" was added; it now reads: Human Leukocyte Antigen (HLA)-matched related donor. 2. Regarding the Note of examples of severe vaso-occlusive crises or events for the criterion that patient had at least four events in the previous 2 years, "An episode of dactylitis (in a patient < 5 years of age" was added. And the fever temperature for acute chest syndrome was changed from 99.5°F to 101.3°F. 3. For the requirement that lists conditions that the patients does not have, a new condition was added: "History of abnormal transcranial doppler, if the patient is < 18 years of age". 4. For the requirement that busulfan is used for myeloablative conditioning, a Note that pharmacokinetically guided busulfan dosing is recommended for myeloablative conditioning was added. 5. For the requirement regarding sickle hemoglobin level and total hemoglobin level, the word "goal" is added and the timepoints were deleted. The new requirements read: Sickle hemoglobin level goal is < 30% of total hemoglobin and total hemoglobin level goal is ≤ 11 g/dL. 6. For the requirement regarding reproductive potential, an option that according to the prescribing physician, the patient is <u>not</u> of reproductive potential was added. The requirements for females and males of reproductive potentiation remain unchanged. **Transfusion-Dependent Beta-Thalassemia:** The following changes were made: 1. For the requirements regarding Human Leukocyte Antigen (HLA)-matched donors, the word "related" was added; it now reads: Human Leukocyte Antigen (HLA)-matched related donor. 2. For the requirement regarding severe iron overload, the Note, specifically regarding high liver iron concentration, was revised as written. Previously it read: high liver iron concentration (≥ 15 mg/g). 3. For the requirement that busulfan is used for myeloablative conditioning, a Note that pharmacokinetically guided busulfan dosing is recommended for myeloablative conditioning was added. 4. For the requirement regarding total hemoglobin level, the word "goal" was added, and the timepoints were deleted. The new requirement reads: Total hemoglobin level goal is ≥ 11 g/dL. 5. For the requirement regarding reproductive potential, an option that according to the prescribing physician, the patient is not of reproductive potential was added. The requirements for females and males of reproductive potentiation remain unchanged. 6. A new requirement that patient does not have "associated alpha-thalassemia and more than one alpha deletion or alpha multiplication or sickle cell beta-thalassemia variant" was added.	09/30/2026

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