Utilization Review Policy 334

POLICY: Hematology – Gene Therapy – Casgevy UM Medical Policy

- Casgevy™ (exagamglogene autotemcel intravenous infusion – Vertex/CRISPR Therapeutics)

EFFECTIVE DATE: 5/15/2024
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COVERAGE CRITERIA FOR: All UCare Plans

OVERVIEW

Casgevy, an autologous hematopoietic stem cell-based gene therapy, is indicated for the following uses:[1]

- **Sickle cell disease** in patients ≥ 12 years of age with recurrent vaso-occlusive crises (VOCs).
- **Transfusion-dependent beta-thalassemia** (TDT) in patients ≥ 12 years of age.

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, which are obtained via apheresis procedure(s).[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. After Casgevy infusion, the edited CD34+ cells engraft in the bone marrow and differentiate to erythroid lineage cells with reduced BCL11A expression. Downregulation of BCL11A expression in the erythroid progenitors of the bone marrow results in reduced BCL11A protein levels, which leads to an increase in γ-globin expression and increased fetal hemoglobin (HbF) production. In patients with TDT, γ-globin production improves the α-globin to non α-globin imbalance, thereby reducing ineffective erythropoiesis and hemolysis and increasing total hemoglobin (Hb) levels, which eliminates the dependence on regular red blood cell (RBC) transfusions. In patients with sickle cell disease, increased HbF levels (≥ 20%) are protective against disease complications, including preventing VOCs.[2]

Disease Overview

Sickle Cell Disease

Sickle cell disease is a group of inherited RBC disorders characterized by the presence of a mutated Hb subunit beta gene.[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 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 mutations 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 is being evaluated in an ongoing, single-dose, multicenter study involving adolescents and adults with sickle cell disease.[1,2,13] Eligible patients underwent mobilization and apheresis procedures to collect CD34+ stem cells for Casgevy manufacturing, followed by myeloablative conditioning with busulfan and infusion of Casgevy. All of the enrolled patients had one of the following genotypes: β^S/β^S, β^S/β^0, or β^S/β^+. In addition, all patients had severe sickle cell disease, as defined by the occurrence of at least two of the following VOC events per year during the 2-year period before screening, while receiving appropriate supportive care: acute pain that required a visit to a medical facility and administration of pain medications (opioids or IV nonsteroidal anti-inflammatory drugs) or RBC transfusions; acute chest syndrome; priapism lasting more than 2 hours and requiring a visit to a medical facility; or splenic sequestration.[1] Key exclusion criteria were patients with the following: clinically significant and active bacterial, viral, fungal, or parasitic infection; advanced liver disease; history or presence of Moyamoya disease; and prior or current malignancy or myeloproliferative disorder or significant immunodeficiency disorder. The primary efficacy set (PES) [n = 31] was composed of patients who received Casgevy infusion and were followed for at least 16 months after infusion. At the interim analysis (June 2023 cut-off date), the median age of patients in the PES was 21 years; 23% of patients were adolescents (≥ 12 and < 18 years of age). At baseline, the annualized (median) rate of severe VOCs during the previous 2 years was 3.5 and the annualized (median) rate of hospitalizations due to severe VOCs during the previous 2 years was 2.0. All patients received plerixafor for mobilization and busulfan for myeloablative conditioning. Casgevy was administered as an IV infusion. The primary efficacy endpoint was the proportion of patients who did not experience a severe VOC for at least 12 consecutive months within the first 24 months after Casgevy infusion (VF12 responders) and the key secondary endpoint was the proportion of patients who did not require hospitalization due to severe VOCs for at least 12 consecutive months within the first 24 months after Casgevy infusion (HF12 responders). Evaluation of both endpoints began 60 days after the last RBC transfusion for post-transplant support or sickle cell disease support. The VF12 response rate was 93.5% (n = 29/31) and all 30 patients evaluable for HF12 response achieved this endpoint.

Transfusion-Dependent Beta-Thalassemia (TDT)

Casgevy is being studied in an ongoing, open-label, multicenter, single-arm study involving adolescents and adults with TDT.[1,14] Eligible patients underwent mobilization and apheresis procedures to collect CD34+ stem cells for Casgevy manufacturing, followed by myeloablative conditioning and Casgevy infusion. Patients were followed for 24 months after Casgevy infusion. All of the enrolled patients had a history of requiring transfusions of 100 mL/kg/year or more of packed RBCs in the 2 years prior to enrollment or requiring at least 10 units/year of packed RBCs in the 2 years prior to enrollment. In addition, patients had one of the following genotypes for beta-thalassemia: β^0/β^0-like (including $\beta^0/\beta^{+[IVS\text{-}I\text{-}110]}$ and $\beta^{+[IVS\text{-}I\text{-}110]}/\beta^{+[IVS\text{-}I\text{-}110]}$) and non-$\beta^0/\beta^0$-like. The PES (n = 35) was composed of patients who received Casgevy infusion and had adequate follow-up for evaluation of the primary efficacy endpoints. At the interim analysis (conducted based on January 2023 data cut-off), the median age of the patients was 20 years; 31.4% of the patients were adolescents (≥ 12 and < 18 years of age).[1] At baseline, the annualized (median) RBC transfusion volume was 205 mL/kg and the annualized (median) number of RBC transfusion episodes was 17. All of the patients received a granulocyte-colony stimulating factor (G-CSF) and plerixafor to mobilize stem cells for apheresis and busulfan for myeloablative conditioning.[1,14] Casgevy (median dose of 7.5×10^6 cells/kg) was administered as an IV infusion. At the interim analysis, the median (minimum, maximum) duration of follow-up was 23.8 (16.1, 48.1) months after Casgevy infusion.[1] The primary efficacy endpoint was the proportion of patients achieving transfusion independence for at least 12 consecutive months (TI12), which was defined as maintaining weighted average Hb ≥ 9 g/dL without RBC transfusions for at least 12 consecutive months, within the first 24 months after Casgevy infusion. Evaluation of this endpoint started 60 days after the last RBC transfusion for post-transplant support or TDT disease management. In total, 32 of 35 patients achieved TI12; the responder rate was 91.4% (98.3% one-sided confidence interval [CI]: 75.7%, 100%). All of the patients who achieved TI12 remained transfusion-independent, with a median duration of 20.8 months and normal mean weighted average total Hb levels of 13.1 g/dL. The median time to last RBC transfusion for patients who achieved TI12 was 30 days after Casgevy infusion. The three patients who did not achieve TI12 had reductions in annualized RBC transfusion volume requirements of 79.8%, 83.9%, and 97.9%, respectively, compared to baseline requirements. In addition, the three patients had reductions in annualized transfusion frequency of 78.6%, 67.4%, and 94.6%, respectively, compared to baseline requirements.

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. 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 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 ≥ 12 years of age; 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 donor; OR
     - **ii.** Patient has an HLA-matched 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
     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 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 [> 99.5°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, and iv):
     - **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. 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

iv. Sickle hemoglobin level will be < 30% of total hemoglobin with total hemoglobin concentration ≤ 11 g/dL at BOTH of the following timepoints (a and b):

a) Prior to planned start of mobilization; AND

b) Until initiation of myeloablative conditioning; 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-lymphotrophic virus-1 and -2 **[documentation required]**; AND

L) According to the prescribing physician, a patient of reproductive potential meets ONE of the following (i or ii):

i. A female† of reproductive potential meets BOTH of the following (a and b):

a) A negative serum pregnancy test will be confirmed prior to the start of each mobilization cycle and re-confirmed prior to myeloablative conditioning; AND

b) Patient will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Casgevy; OR

ii. 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, and P):

A) Patient is ≥ 12 years of age; 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 donor; OR
- **ii.** Patient has an HLA-matched 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):
- **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.** 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
- **ii.** 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); 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.
- **iii.** Busulfan will be used for myeloablative conditioning; AND
- **iv.** Total hemoglobin level is ≥ 11 g/dL at BOTH of the following timepoints (a and b):
  - **a)** Prior to mobilization; AND
  - **b)** Prior to myeloablative conditioning; 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) According to the prescribing physician, a patient of reproductive potential meets ONE of the following (i or ii):
- **i.** A female† of reproductive potential meets BOTH of the following (a and b):
  - **a)** A negative serum pregnancy test will be confirmed prior to the start of each mobilization cycle and re-confirmed prior to myeloablative conditioning; AND
  - **b)** Patient will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Casgevy; OR
- **ii.** 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) The medication is prescribed by a hematologist or a stem cell transplant physician; AND

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

P) If criteria A through O 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.

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.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/31/2024
Selected Revision	**Policy Statement:** The statement regarding verification in claims history for certain criteria was revised to add the qualifier "if claims history is available". The revised statement reads: If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. **Sickle Cell Disease:** **1.** The Note regarding the requirement for no previous gene therapy for sickle cell disease was revised to add the qualifier "(or if claims history is not available)" and to remove "Verify through claims history that the patient has not previously received Casgevy or Lyfgenia (lovotibeglogene autotemcel intravenous infusion)". The revised Note reads: 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. **2.** The criterion regarding cellular screening was revised such that cellular screening is negative for human immunodeficiency virus (HIV)-1 and -2 and negative for Human T-lymphotrophic virus-1 and -2; previously, it was HIV-1 or -2 and Human T-lymphotrophic virus-1 or -2. **3.** In the criterion regarding a male* of reproductive potential, the additional phrase in parenthesis, "(i.e., capable of fathering a child)" was removed (not needed). **4.** The criterion regarding current patient weight was revised to remove the qualifier "before intended receipt of Casgevy". The revised criterion reads: Current patient body weight has been obtained within 30 days **[documentation required]**. **Transfusion-Dependent Beta-Thalassemia:** This condition and criteria for approval were added to the policy. **Conditions Not Recommended for Approval:** For the condition "Prior Receipt of Gene Therapy", Zynteglo (betibeglogene autotemcel intravenous infusion) was added as an example of a gene therapy. Concurrent Use with Reblozyl (luspartercept-aamt subcutaneous injection): This condition was added to the policy.	03/20/2024
Update	**06/28/2024:** In the Policy Statement section, the statement "Some clients have elected Embarc Benefit Protection for Casgevy for the treatment of sickle cell disease; treatment of beta-thalassemia is not part of the Embarc Benefit Protection program" was revised to "Some clients have elected Embarc Benefit Protection". The Casgevy Embarc Benefit Protection includes both indications.	--
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/16/2024
Selected Revision	**Transfusion-Dependent Beta-Thalassemia:** The upper age threshold (< 51 years of age) was removed; the lower age threshold remains: Patient is ≥ 12 years of age. In the Note for the criterion regarding evidence of severe iron overload, the threshold for high liver iron concentration, ≥ 15.5 mg/g, was changed to ≥ 15 mg/g to align with labeling.	09/25/2024
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.	02/05/2025

	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".	
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
UCare P&T Review	Policy reviewed and approved by UCare P&T committee. Annual review process	09/15/2025
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