Drug Coverage Policy

Effective Date.....5/1/2024
Coverage Policy Number.....IP0615
Policy Title .....Casgevy for Sickle Cell Disease

Hematology – Gene Therapy – Casgevy for Sickle Cell Disease

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

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview
Casgevy, an autologous hematopoietic stem cell-based gene therapy, is indicated for the treatment of **sickle cell disease** in patients ≥ 12 years of age with recurrent vaso-occlusive crises (VOCs).[1] Casgevy is also indicated for the treatment of **transfusion-dependent beta-thalassemia** 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 sickle cell disease, increased HbF levels (≥ 20%) are protective against disease complications, including preventing VOCs.[2]

Disease Overview
Sickle cell disease is a group of inherited red blood cell (RBC) disorders characterized by the presence of a mutated hemoglobin (Hb) subunit beta gene.[3-5] 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. 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), Endari® (L-glutamine oral powder), hydroxyurea, and Oxbryta® (voxelotor tablets and tablets for oral suspension).[6-10]

Clinical Efficacy
Casgevy is being evaluated in an ongoing, single-dose, multicenter study involving adolescents and adults with sickle cell disease.[1,2] 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 > 2 hours and requiring a visit to a medical facility; or splenic sequestration. 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] is composed of patients who received Casgevy infusion and were followed for at least 16 months after infusion.[1] 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.

Guidelines
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.[11] 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) 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.

Medical Necessity Criteria

Prior Authorization is recommended for benefit coverage of Casgevy. Approval is recommended for those who meet the **Criteria** and **Dosing** for sickle cell disease.

Review for the indication of beta-thalassemia (transfusion-dependent) is not included in the Embarc Benefit Protection Program.

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, an asterisk (*) 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 for sickle cell disease (approvals and denials) will be forwarded to the Medical Director for evaluation.

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.

Casgevy is considered medically necessary when the following criteria are met:

FDA-Approved Indication

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).

   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, as defined by the following (i, ii, iii, iv, or v):

i. An episode of acute pain that resulted in a visit to a medical facility which required administration of at least ONE of the following (a or b) **[documentation required]**:
   a) Intravenous opioid; OR
   b) Intravenous nonsteroidal anti-inflammatory drug; OR

ii. Acute chest syndrome **[documentation required]**; OR
   Note: Acute chest syndrome 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).

iii. Acute hepatic sequestration **[documentation required]**; OR
   Note: Acute hepatic sequestration 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.

iv. Acute splenic sequestration **[documentation required]**; OR
   Note: Acute splenic sequestration 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.

v. Acute priapism lasting > 2 hours and requiring a visit to a medical facility **[documentation required]**; AND

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 or 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.

   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) Prior to collection of cells for manufacturing, cellular 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, patient 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 Medical Necessity Criteria policy statement.

Dosing. 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).

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Prior Hematopoietic Stem Cell Transplantation.**
   Note: 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. 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). Treatment with Casgevy is not recommended.

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
C9399	Unclassified drugs or biologicals
J3590	Unclassified biologics

References

1. Casgevy™ intravenous infusion [prescribing information]. Waltham, MA: Vertex; January 2024.
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/ncbddd/sicklecell/index.html. Last reviewed July 6, 2023. Accessed on January 29, 2024.
6. Adakveo® intravenous injection [prescribing information]. East Hanover, NJ: Novartis; September 2022.
7. Endari™ oral powder [prescribing information]. Torrance, CA: Emmaus Medical; October 2022.
8. Droxia® capsules [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; January 2022.
9. Siklos® tablets [prescribing information]. Bryn Mawr, PA: Medunik; December 2021.
10. Oxbryta® tablets and tablets for oral suspension [prescribing information]. San Francisco, CA: Global Blood Therapeutics; August 2023.
11. 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.

Revision Details

Type of Revision	Summary of Changes	Date
New	New policy	2/22/2024
Selected Revision	**Updated** 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:** • **Updated:** the Note regarding the requirement for no previous gene therapy for sickle cell disease was	5/1/2024

	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. • **Updated:** 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. • **Updated**: 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). • **Updated**: 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]**.	

The policy effective date is in force until updated or retired.