Blue Cross Blue Shield Blue Care Network of Michigan

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Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

P&T Date: 06/05/2025

Casgevy™ (exagamglogene autotemcel)

HCPCS: J3392

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved indication
   b. FDA approved age
   c. Prescribed by or in consultation with a hematologist
   d. Sickle cell disease
      i. Diagnosis of sickle cell disease (SCD) confirmed either via genetic testing or electrophoresis
      ii. Trial and failure, contraindication, or intolerance to hydroxyurea
      iii. Must have experienced at least 4 severe vaso-occlusive crises in the past 24 months
      iv. Must not have any of the following:
         1. Active infection with HIV-1 or HIV-2, hepatitis B, or hepatitis C
         2. White blood cell count less than 3×10^9/L or platelet count less than 50×10^9/L not related to hypersplenism
         3. Advanced liver disease defined as alanine transferase greater than 3 times the upper limit of normal, total bilirubin greater than 2 times the upper limit of normal, baseline prothrombin time 1.5 times the upper limit of normal, or history of cirrhosis, any evidence of bridging fibrosis, or active hepatitis
         4. Prior treatment with an allogenic stem cell transplant
         5. Prior or current malignancy or immunodeficiency disorder
         6. Must not have received prior treatment with any gene therapy for sickle cell disease or are being considered for treatment with any other gene therapy for sickle cell disease
   e. β-Thalassemia
      i. Genetic testing confirming diagnosis of β-thalassemia
      ii. Must not have α-thalassemia
      iii. Must be considered transfusion dependent with a history of at least 100 mL/kg/year of packed red blood cells (pRBC) in the previous two years OR be managed under standard thalassemia guidelines with ≥ 8 transfusions of pRBCs per year in the previous two years
      iv. Must not have
         1. A prior hematopoietic stem cell transplant (HSCT) or currently be eligible for a HSCT with an HLA matched family donor

2. Active infection with HIV-1 or HIV-2 infection
3. Active immunodeficiency disorder or malignancy
4. Uncorrected bleeding disorder
5. Advanced liver disease defined as
    a) Alanine transferases greater than 3 times the upper limit of normal (ULN) OR
    b) Direct bilirubin greater than 2.5 times the ULN OR
    c) Baseline prothrombin time or partial thromboplastin time greater than 1.5 times the ULN suspected of arising from liver disease OR
    d) Magnetic resonance imaging (MRI) of the liver demonstrating clear evidence of cirrhosis

v. Have not received prior treatment with any gene therapy or are being considered for treatment with any other gene therapy for beta-thalassemia

f. The requesting physician attests to providing clinical outcome information within the appropriate provider portal as requested by BCBSM

g. Trial and failure, contraindication, or intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list

B. Quantity Limitations, Authorization Period and Renewal Criteria
    a. Quantity Limits: Align with FDA recommended dosing
    b. Authorization Period: 12 months with the allowance of only one dose per lifetime
    c. Renewal Criteria: Not applicable as no further authorization will be provided

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Casgevy is an autologous genome edited hematopoietic stem cell-based gene therapy indicated for the treatment of patients 12 years and older with sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs) and transfusion-dependent β-thalassemia (TDT).

- Sickle cell disease

    - Sickle cell disease is a recessive hemolytic anemia caused by a mutation in the β-globin gene. It is characterized by the formation of sickle hemoglobin (HbS). HbS is less soluble and less elastic than fetal hemoglobin (HbF) or normal adult hemoglobin (HbA). The disease involves multicellular adhesion between sickled red blood cells, white blood cells, platelets, and endothelial cells resulting in vaso-occlusive crises (VOCs). VOCs are the hallmark of SCD and are experienced by approximately 70% of patients. They are recurring, unpredictable, painful events that decrease organ function with complications including stroke, pneumonia, vision loss, pulmonary hypertension, leg ulcers, and sepsis. VOCs are often treated as an emergency requiring acute care and are the number one reason patients with SCD visit the emergency room or are hospitalized.

    - Hydroxyurea is a ribonucleotide reductase inhibitor which increases the amount of circulating HbF in the body and has been a mainstay of therapy. It also has been shown to lower the number of circulating leukocytes and reticulocytes altering the expression of adhesion molecules; raise red blood cell (RBC) volume; and improve cellular deformability and rheology, all of which contribute to a decrease in VOCs. The

2014 National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease Guidelines recommend the use of hydroxyurea for the following patient populations:

  - In adults with SCD who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period
  - In adults with SCD who have sickle cell-associated pain that interferes with daily activities and quality of life
  - In adults with SCD who have a history of severe and/or recurrent acute coronary syndrome
  - In adults with SCD who have severe symptomatic chronic anemia that interferes with daily activities or quality of life
  - In infants 9 months of age and older, children, and adolescents with SCD, offer treatment with hydroxyurea regardless of clinical severity to reduce complications
  - In adults and children with SCD who have chronic kidney disease and are taking erythropoietin

- The guidelines recommend starting hydroxyurea at a dose of 15 mg/kg/day for adults and increasing the dose by 5 mg/kg/day every 8 weeks to a maximum dose of 35 mg/kg/day. A clinical response to therapy may take 3 – 6 months. Therefore, a 6 month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy. Guidelines have not yet been updated to include recommendations for use of gene therapy.

- Safety and efficacy for use in SCD were evaluated in the Phase III CLIMB-121 trial, a single arm, multicenter study of 31 patients 18 to 35 years of age with severe SCD and documented βS/βS or βS/β0 genotype. Severe SCD was defined by the occurrence of at least 2 of the following events each year during the 2-year period before screening, while receiving appropriate supportive care (pain management plan, hydroxyurea if indicated): an acute pain event that requires a visit to a medical facility and administration of pain medications (opioids or intravenous [IV] non-steroidal anti-inflammatory drugs [NSAIDs]) or RBC transfusions; acute chest syndrome (ACS), as indicated by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever; priapism lasting greater than 2 hours; and/or splenic sequestration. Participants could not have any of the following: positive presence of HIV-1 or HIV-2, hepatitis B, or hepatitis C; white blood cell count less than 3×10^9/L or platelet count less than 50×10^9/L not related to hypersplenism; advanced liver disease defined as alanine transferase greater than 3 times the upper limit of normal, total bilirubin greater than 2 times the upper limit of normal, baseline prothrombin time 1.5 times the upper limit of normal, or history of cirrhosis, any evidence of bridging fibrosis, or active hepatitis; prior treatment with an allogenic stem cell transplant; and prior or current malignancy or immunodeficiency disorder. The primary endpoint was the proportion of VOC-free responders, defined as patients who did not experience any protocol-defined severe VOCs for at least 12 consecutive months within the first 24 months after Casgevy infusion. The proportion of patients who did not require hospitalization due to severe VOCs for at least 12 consecutive months within the 24-month evaluation period was also assessed. The median (min, max) time to the last RBC transfusion was 19 (11, 52) days following Casgevy infusion. The proportion of VOC-free responders was 93.5% (29/31, 98% one-sided CI: 77.9%, 100.0%). The 29 VOC-free responders did not experience a protocol defined severe VOC during the evaluation period with a median duration of 22.2 months at the time of the interim analysis. One VOC-free responder, after initially achieving a response, experienced an acute pain episode meeting the definition of a severe VOC at month 22.8 requiring a 5-day hospitalization; this patient was reported to have a parvovirus B19 infection at the time. Of the 31 patients evaluable for VOC-free response, one patient was

not evaluable for hospitalization-free response; the remaining 30 patients achieved the endpoint (100% [98% one-sided CI: 87.8%, 100.0%]).

- There is currently no data supporting administration of Casgevy following administration of another gene therapy. Casgevy should not be given following any other gene therapy for SCD as safety and efficacy has not been established.

- Transfusion Dependent β-thalassemia (TDT)

  - The term "thalassemia" refers to a group of blood disorders characterized by a decrease or absence of synthesis of normal hemoglobin globulin chains. According to the chain whose synthesis is impaired, the thalassemias are call α-, β-, γ-, δ-, δβ-, or εγδβ-thalassemias. Beta-thalassemias result from a genetic defect in the HBB gene leading to a reduction in production of β-globulin chains, an excess of α-globulin chains, and a decrease in functioning hemoglobin. Low levels of hemoglobin cause a lack of oxygen in many parts of the body and anemia. People with anemia in beta-thalassemia often require lifelong blood transfusions for survival and subsequent treatment for iron overload due to these transfusions.

  - The 2021 International Thalassemia Federation guidelines for transfusion dependent thalassemias recommend diagnosis should begin with genetic testing because of the extreme diversity in clinical severity of thalassemia subtypes. The degree of excess nonfunctional α-chains is the major predictor of disease severity. The less β-globulin production, the more non-functional α-chains in the bloodstream. β_0-thalassemia refers to the complete absence of production of β-globulin. When patients are homozygous for a β_0-thalassemia gene, they cannot make any normal β-chains. β_+-thalassemia indicates a mutation that presents decreased but not absent production of β-globulin. In thalassemia patients in which one or both of their β-thalassemia mutations are β_+-mutations, the disorder may be less severe. Beta-thalassemia major is a clinical diagnosis referring to a patient who has a severe form of the disease and requires chronic transfusions early in life. Beta-thalassemia intermedia is a clinical diagnosis of a patient characterized by a less severe chronic anemia and a more variable clinical phenotype. Casgevy is not being studied in patients with S/β-thalassemia or α-thalassemia. Patients with other β-thalassemia subtypes that were transfusion dependent are being included in the clinical trial.

  - Treatment guidelines also recommend all patients undergo at least an annual comprehensive assessment at a thalassemia center. During such an assessment, recommendations are summarized after consultation with multiple specialists including a hematologist, a nurse specialist, a hepatologist, a cardiologist, an endocrinologist, a psychologist, a genetics counselor, a social worker, and a dietitian.

  - Blood transfusion is the mainstay of care for individuals with thalassemia major and many with intermedia. The purpose of transfusion is twofold: to improve the anemia and to suppress the ineffective erythropoiesis. Chronic transfusions prevent most of the serious growth, skeletal, and neurological complications of thalassemia major. The decision to start regular transfusions is clear when the initial hemoglobin level is well below 6 g/dL. Continuation of infusions can be assessed by withholding transfusions and monitoring weekly hemoglobin levels. If the hemoglobin drops under 7 g/dL on two occasions two weeks apart, then regular transfusions should be commenced. Guidelines define a patient as transfusion dependent when they are getting infusions of packed red blood cells every 2 – 5 weeks to maintain the pre-transfusion hemoglobin of 9 g/dL - 10.5 g/dL and the post-transfusion hemoglobin less than 14 - 15 g/dL. This translates to approximately 100 mL/kg/year of packed red blood cells.

  - Safety and efficacy were evaluated in the CLIMB-111 trial which included 44 patients with TDT. Participants could not have a prior hematopoietic stem cell transplant (HSCT) or currently be eligible for a HSCT with an HLA matched family donor, presence of HIV-1 or HIV-2 infection, a current immunodeficiency disorder or malignancy, or an uncorrected bleeding disorder. Patients also could not have advanced liver disease

defined as alanine transferases or direct bilirubin greater than 3 times the upper limit of normal (ULN); or baseline prothrombin time or partial thromboplastin time greater than 1.5 times the ULN suspected of arising from liver disease; or magnetic resonance imaging (MRI) of the liver demonstrating clear evidence of cirrhosis. The primary endpoint was the proportion of participants achieving transfusion reduction for at least 6 months. Overall, 42 of 44 patients with TDT stopped red blood cell (RBC) transfusions. The median time since last transfusion was 9.0 (0.8 - 36.2) months, with 16 patients having at least 12 months since their last transfusion. The two patients that had not yet stopped transfusions had 75% and 89% reductions in transfusion volume. By month 3, increases in HbF and mean total hemoglobin levels (> 9 g/dL) were achieved, with mean total hemoglobin levels increasing to and maintained at greater than 11 g/dL thereafter. At month 6, the mean proportion of edited alleles in bone marrow CD34+ hematopoietic stem and progenitor cells (HSPCs) and peripheral blood mononuclear cells was 74.3% and 63.4%, respectively which remained stable in all patients with greater than or equal to 1 year of follow-up.

- There is currently no data supporting administration of Casgevy following administration of another gene therapy. Casgevy should not be given following any other gene therapy for TDT as safety and efficacy has not been established.

References:

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Effective Date: 07/21/2025</td><td>Updated to include the required use of a provider portal to submit clinical outcomes data after Casgevy administration</td></tr>
<tr><td>1.5</td><td>Effective Date: 12/12/2024</td><td>Updated to allow use of electrophoresis for diagnosis of sickle cell disease and changed the authorization period from 6 months to 12 months</td></tr>
<tr><td>1.4</td><td>Effective Date: 04/11/2024</td><td>Updated to include the new FDA approved indication of transfusion-dependent β-thalassemia</td></tr>
<tr><td>1.3</td><td>Effective Date: 02/08/2024</td><td>New policy - replaces previously approved preliminary criteria</td></tr>
<tr><td>1.2</td><td>Effective Date: 01/02/2024</td><td>UM medical management system update for BCNA and MAPPO
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*