Casgevy (exagamglogene autotemcel)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Sickle cell disease (SCD) is an inherited blood disorder caused by a mutation in the beta-globin gene, resulting in abnormal hemoglobin S that polymerizes and causes red blood cells to become rigid and sickle-shaped. This leads to vaso-occlusion (blockage of blood flow through blood vessels), hemolysis (destruction of red blood cells), and endothelial dysfunction, causing acute complications like painful vaso-occlusive crises, acute chest syndrome, and stroke, as well as chronic organ damage. Standard treatment includes hydroxyurea to increase fetal hemoglobin levels, red blood cell transfusions, and more recently, novel targeted therapies like voxelotor (which was withdrawn from the market in September, 2024) and Adakveo (crizanlizumab). However, many patients continue to experience recurrent severe crises despite available therapies. Allogeneic hematopoietic stem cell transplant can be curative but is limited by donor availability and transplant-related risks.

Beta thalassemia is an inherited blood disorder caused by mutations in the beta-globin gene, leading to reduced or absent beta-globin production. In transfusion-dependent beta thalassemia, the severe imbalance in alpha- and beta-globin chains results in ineffective erythropoiesis (creation of red blood cells), severe anemia, and complications from iron overload due to chronic transfusions. Standard treatment is regular red blood cell transfusions and iron chelation therapy. Allogeneic hematopoietic stem cell transplant can be curative but has limitations as in sickle cell disease.

Casgevy (exagamglogene autotemcel) is an autologous ex vivo CRISPR-Cas9 gene-edited hematopoietic stem cell therapy for patients 12 years and older with sickle cell disease with recurrent vaso-occlusive crises or transfusion-dependent beta thalassemia. Casgevy works by disrupting a key erythroid enhancer of the BCL11A gene in autologous hematopoietic stem cells, thereby increasing fetal hemoglobin (HbF) expression and correcting the underlying pathophysiology of these disorders. In sickle cell disease, HbF reduces hemoglobin S concentration, preventing red blood cell sickling, reducing the risk of vaso-occlusive crises. In transfusion-dependent Beta-thalassemia, the increased gamma-globin (a benefit of reducing BCL11A expression) improves the alpha-globin to non-alpha-globin chains, reducing the production of ineffective red blood cells, reducing risk of hemolysis, and increasing hemoglobin (improving anemias). Casgevy (exagamglogene autotemcel) is given as a one-time, single dosage intravenous product.

Definitions

"Beta thalassemia" refers to a group of inherited blood disorders caused by mutations in the beta-globin gene, leading to reduced or absent beta-globin production and an imbalance in alpha- and beta-globin chains, resulting in ineffective erythropoiesis and anemia of varying severity.

"Fetal hemoglobin (HgF)" is the main hemoglobin produced during fetal development and has a higher affinity for oxygen than adult hemoglobin. Increasing fetal hemoglobin expression is a key therapeutic strategy in sickle cell disease and beta thalassemia, as it can inhibit sickle hemoglobin polymerization and compensate for deficient adult beta-globin production.

"Hematopoietic stem cell transplantation" refers to the procedure of infusing hematopoietic stem cells from a donor (allogeneic) or the patient (autologous) to re-establish normal hematopoiesis and potentially cure genetic blood disorders by replacing the patient's defective stem cells with functional ones.

"Karnofsky Performance Status (KPS)" refers to a widely used tool for assessing the functional status of adult patients. It is a scale that ranges from 0 to 100, where 100 represents normal functioning with no complaints or evidence of disease, and 0 represents death.

"Lansky Performance Status (LPS)" refers to a scale designed specifically for assessing the functional status of pediatric patients (typically under 16 years of age). Like the KPS, the LPS ranges from 0 to 100, with 100 representing fully active, normal functioning and 0 representing death.

"Mobilization and apheresis" refers to the process of administering medications (typically G-CSF and plerixafor) to mobilize hematopoietic stem cells from the bone marrow into peripheral blood, followed by collecting the stem cells by apheresis for cell processing and manufacturing of the gene-modified cell therapy product.

"Myeloablative conditioning" refers to high-dose chemotherapy (typically busulfan) given to eliminate the patient's diseased bone marrow and immune system prior to hematopoietic stem cell infusion, creating space for engraftment of the gene-edited cells and minimizing the risk of graft rejection.

"Sickle cell disease" refers to a group of inherited blood disorders caused by a mutation in the beta-globin gene, resulting in abnormal hemoglobin S that polymerizes under deoxygenated conditions, causing red blood cells to become sickle-shaped and prone to hemolysis and vaso-occlusion, leading to a complex pathophysiology involving chronic inflammation, endothelial dysfunction, and end-organ damage.

"Transfusion-dependent beta thalassemia" refers to the most severe phenotype of beta thalassemia (typically beta-zero thalassemia or hemoglobin E/beta-zero thalassemia) in which regular red blood cell transfusions every 2-5 weeks are required to maintain a pre-transfusion hemoglobin level above 9-10 g/dL, prevent complications of anemia and ineffective erythropoiesis, and allow for normal growth and development.

"Vaso-occlusive crisis" refers to the hallmark acute complication of sickle cell disease caused by obstruction of blood flow in the microcirculation by sickled red blood cells, leading to tissue ischemia and severe pain, often requiring hospitalization for pain management, intravenous fluids, and other supportive care. Frequent recurrent vaso-occlusive crises (≥2-3 per year) are a marker of severe disease and an indication for disease-modifying therapies and curative options like stem cell transplantation or gene therapy.

Clinical Indications

Medical Necessity Criteria for Initial Clinical Review

Initial Indication-Specific Criteria

Sickle Cell Disease (SCD) with Recurrent Vaso-occlusive Crises or Transfusion-Dependent β-thalassemia (TDT)

The Plan considers Casgevy (exagamglogene autotemcel) medically necessary when ALL of the following criteria are met:

1. The medication is prescribed by or in consultation with a hematologist or specialist with expertise in sickle cell disease or gene therapies; *AND*
2. The member is 12 years of age or older; *AND*
3. The member meets ONE of the following qualifying diagnoses confirmed by molecular or genetic testing:
    a. Sickle cell disease and meets ALL of the following:
        i. Documented genotype defined as ONE of the following:
            1. βS/βS*; or*
            2. βS/β0*; or*
            3. βS/β+*; or*
            4. Additional genotypes will be considered on a case by case basis (see Appendix A, Table 1)*; and*
        ii. Severe disease characterized by a history of at least 2 severe vaso-occlusive crises per year in the past 2 years despite receiving appropriate supportive care (e.g., hydroxyurea, L-glutamine, voxelotor, crizanlizumab, chronic transfusions). Severe vaso-occlusive crises are defined as ONE of the following:
            1. Acute pain event requiring a medical facility visit and administration of pain medications (e.g., opioids or IV NSAIDs) or RBC transfusion; *or*
            2. Acute chest syndrome, as indicated by a new pulmonary infiltrate with pneumonia-like symptoms, pain, or fever; *or*
            3. Priapism lasting > 2 hours requiring a medical facility visit; *or*
            4. Splenic sequestration, as defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in hemoglobin concentration of ≥2 g/dL; *OR*
    b. Transfusion-dependent beta thalassemia requiring ≥ 100 mL/kg/year or ≥ 10 packed RBC units/year of transfusions within the past 2 years; *AND*
4. The member is an appropriate candidate for hematopoietic stem cell transplantation (HSCT), but does not have an available and suitable, complete HLA-matched related willing donor; *AND*
5. The member meets ALL of the following:
    a. No history of hypersensitivity to dimethyl sulfoxide (DMSO) or dextran 40; *and*

a. No contraindications to the use of plerixafor during the mobilization of hematopoietic stem cells and any contraindications to the use of busulfan and any other medicinal products required during the myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients; *and*
b. No active human immunodeficiency virus type 1 or 2 (HIV-1 and HIV-2), hepatitis B virus (HBV), or hepatitis C (HCV); *and*
c. Not pregnant or breastfeeding; *and*
d. No prior allogeneic or autologous stem cell transplant or gene therapy (Casgevy or any other) for the requested diagnosis; *and*
e. No significant organ dysfunction defined as ALL of the following as applicable:
    i. Liver: direct bilirubin > 2.5 times the upper limit of normal (ULN), aspartase transaminase or alanine transaminase > 3 times ULN, or bridging fibrosis or cirrhosis on liver biopsy; *and*
    ii. Kidney: estimated glomerular filtration rate < 60 mL/min/1.73 m^2; *and*
    iii. Heart (TDT only): Cardiac T2* < 10 ms by MRI or LVEF < 45% by ECHO; *and*
f. For sickle cell disease, the member meets ALL of the following as applicable:
    i. For age 12-16 years: no abnormal transcranial Doppler velocity ≧ 200 cm/sec; *or*
    ii. Does not have untreated or high-risk Moyamoya syndrome; *AND*

6. Prescriber attests that:
    a. Disease-modifying therapies and iron chelation will be discontinued at the specified intervals before cell collection and conditioning:
        i. all disease-modifying therapies (e.g. hydroxyurea, voxelotor, crizanlizumab) at least 8 weeks prior to mobilization.
        ii. iron chelation at least 7 days prior to conditioning.
    b. back-up collection of ≥ 2 x 10^6 unmodified CD34+ rescue cells/kg will be collected and cryopreserved prior to myeloablative conditioning; *AND*
    c. The minimum recommended dose is 3.0 × 10^6 CD34+ cells/kg.

If the above prior authorization criteria are met, Casgevy (exagamglogene autotemcel) will be authorized as a one-time 18-months approval for a single infusion.

Continued Care

Medical Necessity Criteria for Subsequent Clinical Review

Subsequent Medical Necessity Criteria

Sickle Cell Disease (SCD) with Recurrent Vaso-occlusive Crises or Transfusion-Dependent β-thalassemia (TDT)

There are no medical necessity criteria for reauthorization of Casgevy (exagamglogene autotemcel). The FDA label specifies Casgevy as a single-dose gene therapy. Casgevy is intended to be a one-time gene therapy. It is expected to provide durable, potentially life-long effects with a single infusion by

addressing the underlying genetic cause of sickle cell disease or transfusion-dependent beta thalassemia.

In clinical trials, a single infusion of Casgevy demonstrated sustained efficacy in eliminating severe vaso-occlusive crises in sickle cell disease and transfusion requirements in beta thalassemia for the duration of follow-up (at least 2 years and up to 4 years). There is no evidence to support the safety or efficacy of repeat administration.

Experimental or Investigational / Not Medically Necessary

Casgevy (exagamglogene autotemcel) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Re-treatment [Casgevy (exagamglogene autotemcel) is indicated for one-time single-dose intravenous use only. There is no evidence to support the safety or efficacy of repeat administration.]
- Use in pediatric members aged less than 12 years [The safety and efficacy of Casgevy (exagamglogene autotemcel) in pediatric patients aged less than 12 years has not been established.]
- Use in members who do not meet the specified clinical criteria for sickle cell disease severity or transfusion-dependence in beta thalassemia [Casgevy has only been studied in patients with severe, frequently symptomatic disease that is inadequately managed with available therapies.]
- Use in members with significant comorbidities or organ dysfunction that would preclude safe administration of myeloablative conditioning and hematopoietic stem cell transplantation [Certain pre-existing conditions increase the risk of serious complications and were excluded from clinical trials.]
- Use as salvage therapy after failure of allogeneic stem cell transplantation or a different gene therapy [The efficacy and safety of Casgevy in these contexts have not been established, and re-treatment would carry additional risks.]
- Prophylactic use to prevent sickle cell disease complications in asymptomatic individuals or those with infrequent, mild symptoms [The risk-benefit balance may not be favorable in low-risk patients given the intensive nature of the treatment and potential for adverse effects.]

Applicable Billing Codes

Service(s) name	
CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*

96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
96367	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); additional sequential infusion of a new drug/substance, up to 1 hour (List separately in addition to code for primary procedure)
96368	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); concurrent infusion (List separately in addition to code for primary procedure)
96374	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug
96376	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of the same substance/drug provided in a facility (List separately in addition to code for primary procedure)
96409	Chemotherapy administration; intravenous, push technique, single or initial substance/drug
J3392	Injection, exagamglogene autotemcel, per treatment
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*
D56.1	Beta Thalassemia
D56.5	Hemoglobin E-beta thalassemia
D57.00	Hb-Ss Disease With Crisis, Unspecified
D57.01	Hb-Ss Disease With Acute Chest Syndrome
D57.02	Hb-Ss Disease With Splenic Sequestration
D57.03	Hb-Ss Disease With Cerebral Vascular Involvement
D57.04	Hb-Ss Disease With Dactylitis
D57.09	Hb-Ss Disease With Crisis With Other Specified Complication
D57.1	Sickle-Cell Disease Without Crisis
D57.20	Sickle-Cell/Hb-C Disease Without Crisis
D57.211	Sickle-Cell/Hb-C Disease With Acute Chest Syndrome

D57.212	Sickle-Cell/Hb-C Disease With Splenic Sequestration
D57.213	Sickle-Cell/Hb-C Disease With Cerebral Vascular Involvement
D57.214	Sickle-Cell/Hb-C Disease With Dactylitis
D57.218	Sickle-Cell/Hb-C Disease With Crisis With Other Specified Complication
D57.219	Sickle-Cell/Hb-C Disease With Crisis, Unspecified
D57.40	Sickle-Cell Thalassemia Without Crisis
D57.411	Sickle-Cell Thalassemia, Unspecified, With Acute Chest Syndrome
D57.412	Sickle-Cell Thalassemia, Unspecified, With Splenic Sequestration
D57.413	Sickle-Cell Thalassemia, Unspecified, With Cerebral Vascular Involvement
D57.414	Sickle-Cell Thalassemia, Unspecified, With Dactylitis
D57.418	Sickle-Cell Thalassemia, Unspecified, With Crisis With Other Specified Complication
D57.419	Sickle-Cell Thalassemia, Unspecified, With Crisis
D57.42	Sickle-Cell Thalassemia Beta Zero Without Crisis
D57.431	Sickle-Cell Thalassemia Beta Zero With Acute Chest Syndrome
D57.432	Sickle-Cell Thalassemia Beta Zero With Splenic Sequestration
D57.433	Sickle-Cell Thalassemia Beta Zero With Cerebral Vascular Involvement
D57.434	Sickle-Cell Thalassemia Beta Zero With Dactylitis
D57.438	Sickle-Cell Thalassemia Beta Zero With Crisis With Other Specified Complication
D57.439	Sickle-Cell Thalassemia Beta Zero With Crisis, Unspecified
D57.44	Sickle-Cell Thalassemia Beta Plus Without Crisis
D57.451	Sickle-Cell Thalassemia Beta Plus With Acute Chest Syndrome
D57.452	Sickle-Cell Thalassemia Beta Plus With Splenic Sequestration
D57.453	Sickle-Cell Thalassemia Beta Plus With Cerebral Vascular Involvement
D57.454	Sickle-Cell Thalassemia Beta Plus With Dactylitis
D57.458	Sickle-Cell Thalassemia Beta Plus With Crisis With Other Specified Complication
D57.459	Sickle-Cell Thalassemia Beta Plus With Crisis, Unspecified
D57.80	Other Sickle-Cell Disorders Without Crisis

D57.811	Other Sickle-Cell Disorders With Acute Chest Syndrome
D57.812	Other Sickle-Cell Disorders With Splenic Sequestration
D57.813	Other Sickle-Cell Disorders With Cerebral Vascular Involvement
D57.814	Other Sickle-Cell Disorders With Dactylitis
D57.818	Other Sickle-Cell Disorders With Crisis With Other Specified Complication
D57.819	Other Sickle-Cell Disorders With Crisis, Unspecified
H36.811	Nonproliferative sickle-cell retinopathy, right eye
H36.812	Nonproliferative sickle-cell retinopathy, left eye
H36.813	Nonproliferative sickle-cell retinopathy, bilateral
H36.819	Nonproliferative sickle-cell retinopathy, unspecified eye
H36.821	Proliferative sickle-cell retinopathy, right eye
H36.822	Proliferative sickle-cell retinopathy, left eye
H36.823	Proliferative sickle-cell retinopathy, bilateral
H36.829	Proliferative sickle-cell retinopathy, unspecified eye
O35.2XX0	Maternal care for (suspected) hereditary disease in fetus, not applicable or unspecified
O99.019	Anemia complicating pregnancy, unspecified trimester
P09.3	Abnormal findings on neonatal screening for congenital hematologic disorders

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Appendix A

Table 1: Additional Sickle Cell Disease-Related Genotypes

Condition	B-globulin genotype
Hemoglobin SC	Inheriting one HbS gene and one HbC gene, Hemoglobin (Hb) SC disease, βSβC
Hemoglobin SD	Inheriting one HbS gene and one HbD gene, Hb SD disease, βSβD
Hemoglobin SE	Inheriting one HbS gene and one HbE gene, Sickle-hemoglobin E disease, βSβE
Hemoglobin SO	Inheriting one HbS gene and one HbO gene, Hemoglobin SO disease, βSβO

Clinical Guideline Revision / History Information

Original Date: 3/21/2024
Reviewed/Revised: 7/1/2025, 10/01/2025, 12/01/2025