Oscar Clinical Guideline: Lyfgenia (lovotibeglogene autotemcel) (CG114, Ver. 3)

Lyfgenia (lovotibeglogene autotemcel)

Summary

Sickle cell disease (SCD) is an inherited blood disorder caused by mutations in the beta-globin gene, resulting in production of 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 (VOCs) or events (VOEs), acute chest syndrome (ACS), and stroke, as well as chronic organ damage. Standard treatment includes hydroxyurea to increase fetal hemoglobin levels, red blood cell transfusions, and more recently, targeted therapies like voxelotor

(which was withdrawn from the market in September, 2024) and Adakveo (crizanlizumab). However, many individuals continue to experience recurrent severe crises despite available therapies. Allogeneic hematopoietic stem cell transplant (HSCT) can be curative but is limited by donor availability and transplant-related risks (i.e., graft-versus-host disease, graft failure, transplanatation-related mortality).

Lyfgenia (lovotibeglogene autotemcel) is an autologous ex vivo lentiviral vector gene addition therapy for those 12 years and older with SCD and a history of VOEs. Lyfgenia (lovotibeglogene autotemcel) works by adding functional copies of a modified beta-globin gene into autologous hematopoietic stem cells, leading to production of anti-sickling hemoglobin and reduction of sickle hemoglobin, thus correcting the underlying pathophysiology of SCD.

Definitions

"Acute Chest Syndrome" is defined as an acute event with pneumonia-like symptoms (e.g., chest pain, fever [>38.5℃], tachypnea, wheezing or cough, or findings upon lung auscultation).

"Acute hepatic sequestration" is a sudden increase in liver size associated with pain in the right upper quadrant, abnormal results of liver-function test and reduction in hemoglobin.

"Acute splenic sequestration" is a sudden enlargement of the spleen and reduction in hemoglobin.

"Fetal hemoglobin" 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 SCD, 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 individual (autologous) to re-establish normal hematopoiesis and potentially cure genetic blood disorders by replacing the individual's defective stem cells with functional ones.

"Karnofsky Performance Status (KPS)" refers to a widely used tool for assessing the functional status of adults. 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 individuals (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 individual'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.

"Priapism" is defined as a sustained, unwanted painful erection lasting more than 2 hours.

"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.

"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 Clinical Review

Indication-Specific Criteria

Sickle Cell Disease

The Plan considers Lyfgenia (lovotibeglogene 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 has sickle cell disease (SCD) with documented βS/βS, βS/β0, or βS/β+ genotype confirmed by molecular or genetic testing; *AND*
4. The member has severe SCD, defined as experiencing at least 4 severe vaso-occlusive events (VOEs) in the past 24 months despite appropriate supportive care measures (e.g., pain management plan). Severe VOEs are characterized by any of the following:
    a. An episode of acute pain with no medically determined cause other than vaso-occlusion, requiring a ≥ 24-hour hospital or emergency room(ER) observation unit visit, or at least 2

visits to a day unit or ER over 72 hours with both visits requiring intravenous treatment (e.g., opioids, non-steroidal anti-inflammatory drugs, red blood cell transfusion); *and/or*

b. Acute chest syndrome (ACS); *and/or*
c. Acute hepatic sequestration; *and/or*
d. Acute splenic sequestration; *and/or*
e. Priapism episodes requiring a medical facility visit (inpatient admission not required); *AND*

5. The member is an appropriate candidate for hematopoietic stem cell transplantation (HSCT) but does not have an available and suitable, complete HLA-matched related donor; *AND*
6. For members ≥16 years of age, Karnofsky performance status ≥60%, or for members <16 years of age, Lansky performance status ≥60%; *AND*
7. The member meets ALL of the following:
    a. No evidence of a history of hypersensitivity to dimethyl sulfoxide (DMSO) or dextran 40; *and*
    b. No evidence of advanced liver disease, defined as:
        i. Baseline prothrombin time or partial thromboplastin time >1.5 times upper limit of normal, suspected due to liver disease; *or*
        ii. Clear evidence of liver cirrhosis, active hepatitis or significant fibrosis (based on Magnetic resonance imaging [MRI] or liver biopsy); *or*
        iii. Liver iron concentration ≥15 mg/g unless liver biopsy shows no evidence of cirrhosis, active hepatitis or significant fibrosis; *or*
        iv. Persistent aspartate transaminase (AST), alanine transaminase (ALT), or direct bilirubin >3 times upper limit of normal; *and*
    c. No evidence of a contraindication 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*
    d. No evidence of clinically significant and active bacterial, viral, fungal, or parasitic infection; *and*
    e. No evidence of a history of severe cerebral vasculopathy, defined as:
        i. Overt or hemorrhagic stroke; *or*
        ii. Abnormal transcranial Doppler velocity ≥200 cm/sec requiring chronic transfusion; *or*
        iii. Occlusion or stenosis in the polygon of Willis; *or*
        iv. Presence of Moyamoya disease; *and*

        (Note: silent cerebral infarcts in the absence of above criteria are allowed).
    f. No evidence of inadequate bone marrow function, defined as absolute neutrophil count <1000/µL (<500/µL if on hydroxyurea) or platelet count <100,000/µL; *and*
    g. No evidence of the positive for presence of human immunodeficiency virus type 1 or 2 (HIV-1 and HIV-2), hepatitis B virus (HBV), or hepatitis C (HCV); *and*

h. Presence of genetic mutations that result in the inactivation of 2 or more α-globin genes (-α3.7/-α3.7); *and*
i. No evidence of a prior allogeneic or autologous stem cell transplant or gene therapy for sickle cell disease (Lyfgenia or any other); *and*
j. No evidence of pregnancy or breastfeeding; *and*
k. No evidence of renal impairment (defined as creatinine clearance ≤ 70 mL/min/1.73 m^2); *AND*

8. Prescriber attests that:
    a. Disease-modifying therapies and iron chelation will be discontinued at the specified intervals before cell collection and conditioning:
        i. disease-modifying therapies (e.g. L-glutamine, voxelotor and crizanlizumab) at least 8 weeks prior to mobilization.
        ii. iron chelation at least 7 days prior to conditioning.
    b. back-up collection of ≥ 1.5 x 10^6 unmodified CD34+ rescue cells/kg will be collected and cryopreserved prior to myeloablative conditioning; *AND*
9. Dose is within the recommended range of:
    a. Minimum of 3.0 × 10^6 CD34+ cells/kg*; and*
    b. Maximum of 14.0 x 10^6 CD34+ cells/kg.

<u>If the above prior authorization criteria are met, Lyfgenia (lovotibeglogene autotemcel) will be authorized for one dose per lifetime, with an approval duration of 6 months.</u>

Continued Care

Medical Necessity Criteria for Reauthorization

Subsequent Indication-Specific Criteria

<u>Sickle Cell Disease</u>

There are no medical necessity criteria for reauthorization of Lyfgenia (lovotibeglogene autotemcel). Lyfgenia (lovotibeglogene autotemcel) is intended as a one-time gene therapy for the treatment of sickle cell disease. The FDA-approved prescribing information specifies that Lyfgenia is for single-dose intravenous infusion only. It is expected to provide durable, potentially lifelong effects with a single treatment by addressing the underlying genetic cause of sickle cell disease.

There is currently no evidence to support the safety or efficacy of repeat administration of Lyfgenia (lovotibeglogene autotemcel). Re-treatment with the same or a different gene therapy after initial administration of Lyfgenia (lovotibeglogene autotemcel) has not been studied and may carry additional safety risks. Therefore, coverage of Lyfgenia (lovotibeglogene autotemcel) is limited to a single one-time infusion per lifetime under the Plan policy. Reauthorization requests for repeat treatment will be considered not medically necessary.

Experimental or Investigational / Not Medically Necessary

Lyfgenia (lovotibeglogene 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 [Lyfgenia [lovotibeglogene 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 members less than 12 years of age (The safety and efficacy of Lyfgenia [lovotibeglogene autotemcel] in those less than 12 years of age has not been established).
- Members with VOC frequency that does not meet the specified threshold for severe SCD in clinical trials (Lyfgenia [lovotibeglogene autotemcel] has only been studied in those 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 HSCT (Certain pre-existing conditions increase the risk of serious complications and were excluded from clinical trials).
- Use as salvage therapy after failure of allogeneic HSCT or a different gene therapy (he efficacy and safety of Lyfgenia [lovotibeglogene autotemcel] in these contexts have not been established, and re-treatment would carry additional risks).
- Prophylactic use to prevent SCD complications in asymptomatic individuals or those with infrequent, mild symptoms (the risk-benefit balance may not be favorable in low-risk individuals given the intensive nature of the treatment and potential for adverse effects).

Applicable Billing Codes

Table 1	
CPT/HCPCS codes for Sickle Cell Disease 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)

38241	Hematopoietic progenitor cell (HPC); autologous transplantation
J3394	Injection, lovotibeglogene autotemcel, per treatment

Table 2	
ICD-10 codes considered medically necessary for Sickle Cell Disease with Table 1 (CPT/HCPCS) codes if criteria are met:	
Code	*Description*
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, wWith Ccrisis wWith oOther sSpecified cComplication
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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