Corporate Medical Policy: Lovotibeglogene autotemcel (Lyfgenia®) **"Notification"** **POLICY EFFECTIVE DECEMBER 15, 2025**

Restricted Product(s):

- lovotibeglogene autotemcel (Lyfgenia®) intravenous infusion for administration by a healthcare professional

FDA Approved Use:

- For the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events
- Limitations of use:
  - Following treatment with this product, patients with α-thalassemia trait (-α3.7/-α3.7) may experience anemia with erythroid dysplasia that may require chronic red blood cell transfusions. This product has not been studied in patients with more than two α-globin gene deletions

Criteria for Medical Necessity:

The restricted product(s) may be considered medically necessary when the following criteria are met:

1. The patient is 12 to 50 years of age; **AND**
2. The patient has a diagnosis of **sickle cell disease (SCD) [medical record documentation required]**; **AND**
3. The diagnosis has been confirmed by BOTH of the following:
   a. ONE of the following:
      i. Identification of significant quantities of HbS with or without an additional abnormal β-globin chain variant by hemoglobin assay **[medical record documentation required]**; **OR**
      ii. Identification of biallelic *HBB* pathogenic variants where at least one allele is the p.Glu6Val pathogenic variant on molecular genetic testing **[medical record documentation required]**; **AND**
   b. Molecular genetic testing demonstrating ONE of the following genotypes:
      i. β^S/β^S or β^S/β^0 or β^S/β^+ genotype **[medical record documentation required]**; **OR**
      ii. The prescriber has submitted written clinical rationale to support that use of the requested agent is clinically appropriate for the patient's genotype and disease severity **[medical record documentation required]**; **AND**
4. The patient has experienced at least four severe vaso-occlusive events (VOEs)*** in the past 24 months in the setting of appropriate supportive care measures for SCD (e.g., pain management plan) **[medical record documentation required]**; **AND**
5. ONE of the following:
   a. The patient has uncontrolled disease despite treatment with hydroxyurea OR crizanlizumab at any point in the past **[medical record documentation required]**; **OR**

   b. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to hydroxyurea AND crizanlizumab **[medical record documentation required]**; **AND**
6. The patient will discontinue any disease-modifying therapies for SCD (e.g., crizanlizumab, hydroxyurea, voxelotor) at least 8 weeks prior to the planned start of hematopoietic stem cell (HSC) mobilization and myeloablative conditioning **[medical record documentation required]**; **AND**
7. The patient is clinically fit to undergo autologous hematopoietic stem cell transplantation **[medical record documentation required]**; **AND**
8. The patient has NOT received prior allogeneic hematopoietic stem cell transplantation **[medical record documentation required]**; **AND**
9. If the patient is less than 18 years of age, the patient is a candidate for an allogeneic hematopoietic cell transplantation but has NO available suitable and willing 10/10 human leukocyte antigen (HLA)-matched sibling hematopoietic-cell donor **[medical record documentation required]**; **AND**
10. The patient has adequate bone marrow function, as defined by an absolute neutrophil count of 1,000/µL or greater (500/µL or greater for patients on hydroxyurea therapy) or a platelet count of 100,000/µL or greater **[medical record documentation required, including lab tests within the past 3 months]**; **AND**
11. The patient is able to receive red blood cell (RBC) transfusions **[medical record documentation required]**; **AND**
12. The patient does NOT have severe cerebral vasculopathy, including ONE or more of the following **[medical record documentation required]**:
    a. Any history of overt ischemic or hemorrhagic stroke; **OR**
    b. More than 50% stenosis or occlusion in the circle of Willis; **OR**
    c. Presence of Moyamoya disease; **AND**
13. The patient does NOT have advanced liver disease, including ONE or more of the following **[medical record documentation required]**:
    a. Clear evidence of liver cirrhosis, active hepatitis, or significant fibrosis; **OR**
    b. Liver iron concentration of 15 mg/g or greater unless liver biopsy shows no evidence of cirrhosis, active hepatitis, or significant fibrosis; **AND**
14. The patient does NOT have any evidence of chronic kidney disease **[medical record documentation required]**; **AND**
15. The patient does NOT have a history of iron overload demonstrated by cardiac T2* less than 10 msec by magnetic resonance imaging (MRI) or left ventricular ejection fraction (LVEF) less than 45% by echocardiogram **[medical record documentation required]**; **AND**
16. The patient does NOT have clinically significant pulmonary hypertension prior to starting treatment with the requested agent **[medical record documentation required]**; **AND**
17. The patient does NOT have presence of genetic mutations that result in the inactivation of 2 or more α-globin genes **[medical record documentation required]**; **AND**
18. The patient is NOT human immunodeficiency virus type 1 or 2 (HIV-1 or HIV-2) positive **[medical record documentation required, including lab tests within the past 3 months]**; **AND**
19. ONE of the following **[medical record documentation required, including lab results within the past 3 months]**:
    a. The patient's hepatitis B surface antigen is negative; **OR**

   b. The patient has been previously vaccinated against hepatitis B virus (HBV) (i.e., HBV surface antibody [Ab]-positive) AND is negative for other markers of prior HBV infection (e.g., negative for HBV core Ab); **OR**
   c. The patient is negative for HBV DNA; **AND**
20. ONE of the following **[medical record documentation required, including lab results within the past 3 months]**:
   a. The patient's hepatitis C virus (HCV) antibody is negative; **OR**
   b. The patient's HCV antibody is positive AND the patient's HCV viral load is undetectable; **AND**
21. The patient does NOT have any prior or current malignancy or immunodeficiency disorder, with the exception of non-melanoma skin cancers, nor have any immediate family members with a known or suspected Familial Cancer Syndrome **[medical record documentation required]**; **AND**
22. The patient does NOT have any clinically significant and active bacterial, viral, fungal, or parasitic infection **[medical record documentation required]**; **AND**
23. The patient does NOT have any contraindications to use of plerixafor during the mobilization of hematopoietic stem cells nor any contraindications to use of busulfan and any other medications required during the myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients **[medical record documentation required]**; **AND**
24. The patient has NOT received any previous gene therapy for the requested and/or approved indications, including the requested agent **[medical record documentation required]**; **AND**
25. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist, transplant specialist) or has consulted with a specialist in the area of the patient's diagnosis **[medical record documentation required]**; **AND**
26. The requested dose is within FDA labeled dosing for the requested indication, and the requested quantity does NOT exceed the maximum units allowed for the duration of approval (see table below) **[medical record documentation required]**.

Duration of Approval: 365 days (1 year); one-time, single-dose treatment per lifetime

** Please note, for certain identified gene and cellular therapies such as lovotibeglogene autotemcel (Lyfgenia®), when coverage is available and the individual meets medically necessary criteria, distribution from a specialty pharmacy provider due to cost (distribution channel restriction) may be required in order for coverage to be provided. **Please contact BCBS NC** to coordinate this therapy.

***A severe VOE is defined as an acute episode of pain with no medically determined cause other than a 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. One exception being that priapism does not require hospital admission but does require a medical facility visit; 4 priapism episodes that require a visit to a medical facility (without inpatient admission) are sufficient to meet criterion for severe VOE. Severe VOEs may include acute chest syndrome, acute hepatic sequestration, acute splenic sequestration, and/or acute priapism requiring care at a medical facility.

FDA Label Reference				
Medication	**Indication**	**Dosing**	**HCPCS**	**Maximum Units***
lovotibeglogene autotemcel (Lyfgenia®) intravenous (IV) infusion	Sickle cell disease in patients ≥12 years old with a history of vaso-occlusive events	IV: Minimum recommended dose of 3 x 10^6 CD34+ cells per kg of body weight, as a single dose	J3394	**1**

***Maximum units allowed for duration of approval**

References: all information referenced is from FDA package insert unless otherwise noted below.

1. 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(18):3668–3689.
2. Kanter J, Thompson AA, Piercley FJ Jr, et al. Lovo-cel gene therapy for sickle cell disease: Treatment process evolution and outcomes in the initial groups of the HGB-206 study. *Am J Hematol*. 2023 Jan;98(1):11-22.
3. Kanter J, Walters MC, Krishnamurti L, et al. Biologic and clinical efficacy of LentiGlobin for sickle cell disease. *N Engl J Med*. 2022;386(7):617-628.

Policy Implementation/Update Information: Criteria and treatment protocols are reviewed annually by the Blue Cross NC P&T Committee, regardless of change. This policy is reviewed in Q2 annually.

December 2025: Criteria change: Added diagnostic confirmation criteria of either presence of significant quantities of HbS with or without an additional abnormal β-globin chain variant on hemoglobin assay OR molecular genetic testing showing biallelic *HBB* pathogenic variants with at least one allele as the p.Glu6Val pathogenic variant. Updated genotype-specific requirement to allow for prescriber submission of adequate written clinical rationale to support use of the requested agent for the patient's genotype and disease severity. Adjusted required trial and failure of hydroxyurea (HU) to specify uncontrolled disease despite treatment with HU or crizanlizumab at any point in the past. Added required discontinuation of any disease-modifying therapies for SCD at least 8 weeks prior to mobilization and conditioning. Removed Karnofsky/Lansky performance status defining ability to undergo autologous HSCT. Adjusted criteria to only apply to patients less than 18 years old for allogeneic HSCT candidate but no available suitable and willing 10/10 HLA-matched sibling hematopoietic-cell donor. Reformatted criteria for no history of iron overload to add LVEF < 45% as additional indication of iron overload. Adjusted no HBV criteria for

clarity to allow for vaccinated patients (HBV surface antibody-positive) who are negative for other HBV markers (HBV core antibody-negative) and for past HBV exposure if patient is negative for HBV DNA. Adjusted HCV antibody-positive criteria with negative HCV RNA to undetectable viral load for clarity. Added that no previous gene therapy requirement is for the requested and/or approved indications. Other minor updates made throughout policy for clarity. **Policy notification given 10/15/2025 for effective date 12/15/2025**.
July 2024: Coding change: Added HCPCS code J3394 to dosing reference table effective 7/1/2024; deleted C9399, J3490, and J3590 termed 6/30/2024.
January 2024: Original medical policy criteria issued.