MEDICAL COVERAGE POLICY	
SERVICE:	**Lyfgenia™ (Lovotibeglogene autotemcel)**
Policy Number:	**311**
Effective Date:	**07/01/2025**
Last Review:	**06/09/2025**
Next Review:	**06/08/2026**

Important note: *Unless otherwise indicated, medical policies will apply to all lines of business. Medical necessity as defined by this policy does not ensure the benefit is covered. This medical policy does not replace existing federal or state rules and regulations for the applicable service or supply. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan documents. See the member plan specific benefit plan document for a complete description of plan benefits, exclusions, limitations, and conditions of coverage. In the event of a discrepancy, the plan document always supersedes the information in this policy.*

SERVICE: Lovotibeglogene autotemcel (Lyfgenia™)

PRIOR AUTHORIZATION: Required

POLICY: Please review the plan's EOC (Evidence of Coverage) or Summary Plan Description (SPD) for details.

For Medicare plans, please refer to appropriate Medicare NCD (National Coverage Determination) or LCD (Local Coverage Determination). If there are no applicable NCD or LCD criteria, use the criteria set forth below.

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid Provider Procedures Manual | TMHP (TMPPM). Texas Mandate HB154 is applicable for Medicaid plans.

Baylor Scott & White Health Plan (BSWHP) may consider lovotibeglogene autotemcel (Lyfgenia™) medically necessary when documentation is submitted showing ALL of the following criteria are met:

1. Member has a contraindication to exagamglogene (Casgevy™); **AND**
2. Lovotibeglogene is being prescribed by or in consultation with a board-certified hematologist; **AND**
3. Member is 12 years of age or older, but less than or equal to 50 years of age; **AND**
4. Member has a Karnofsky performance status of ≥60% for subjects ≥16 years of age or Lansky performance status of ≥60% for subjects <16 years of age; **AND**
5. Member has a diagnosis of Sickle Cell Disease (SCD) with one of the following genotypes confirmed by molecular or genetic testing:
   a) β^S/β^S
   b) β^S/β^0
   c) β^S/β^+

   AND
6. Provider attests member will receive lovotibeglogene at an activated qualified treatment center; **AND**
7. Member has experienced hydroxyurea failure, intolerance, or has a contraindication; **AND**
8. Member is eligible for autologous hematopoietic stem cell transplant (aHSCT); **AND**
9. Member does NOT have an available human leukocyte antigen (HLA)-matched related donor; **AND**

10. Member has NOT received any of the following:
    a) Hematopoietic stem cell transplant (HSCT)
    b) Lovotibeglogene or any other gene therapy for SCD
    c) Investigational cellular therapy for SCD; **AND**
11. Lovotibeglogene will NOT be used concomitantly with other gene editing therapies for SCD; **AND**
12. Lovotibeglogene will be dosed and administered according to FDA approved labeling; **AND**
13. Member has experienced ≥4 severe vaso-occlusive events (sVOE) over the previous 2 years while receiving appropriate supportive care (e.g., pain management plan). Severe vaso-occlusive episode (sVOE) defined as any of the following:

    a) Acute pain events that required a visit to a medical facility and administration of pain medications (opioids or intravenous non-steroidal anti-inflammatory drugs) or RBC transfusions
    b) Acute chest syndrome, as indicated by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever
    c) Priapism lasting >2 hours and requiring a visit to a medical facility
    d) Splenic sequestration, as defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in hemoglobin concentration of ≥2 g/dL
    e) Acute hepatic sequestration, 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 reduction in Hb concentration by ≥2 g/dL below the baseline value

    AND
14. Member does NOT have any of the following:
    a) Absolute neutrophil count of $<1\times10^9$/L ($<0.5\times10^9$/L for subjects on hydroxyurea)
    b) Platelet count $<100\times10^9$/L
    c) Baseline left ventricular ejection fraction (LVEF) <45% by echocardiogram
    d) Baseline estimated glomerular filtration rate <70 mL/min/1.73 m2
    e) History of iron overload or serum ferritin levels >1000 ng/mL and a cardiac MRI T2*<10 ms
    f) Advanced liver disease, as defined by any one of the following:
        I. Persistent aspartate transaminase, alanine transaminase, or direct bilirubin value >3× the upper limit of normal (ULN)
        II. Baseline prothrombin time or partial thromboplastin time >1.5 × ULN, suspected of arising from liver disease
        III. MRI of the liver demonstrating clear evidence of cirrhosis
        IV. If ineligible for liver biopsy the flowing MRI findings are exclusionary:
            1) MRI findings suggestive of active hepatitis
            2) Significant fibrosis
            3) Inconclusive evidence of cirrhosis
            4) Liver iron concentration ≥15 mg/g

V. If eligible for liver biopsy and MRI findings are suggestive of active hepatitis, significant fibrosis, inconclusive evidence of cirrhosis, or liver iron concentration ≥15 mg/g any evidence of the following upon liver biopsy are exclusionary:
   1) Cirrhosis
   2) Bridging fibrosis
   3) Significant active hepatitis

g) Clinically significant, active bacterial, viral, fungal, or parasitic infection
h) Any prior or current malignancy except previously treated, non-life threatening, cured tumors
i) Any prior or current immunodeficiency disorder
j) Positive for presence of HIV-1 or HIV-2, hepatitis B DNA (HBV DNA), or human T-lymphotropic virus-1 or -2
k) Detectable hepatitis C viral load
l) More than two α-globin gene deletions
m) Unable to receive RBC transfusion
n) Contraindication to plerixafor, busulfan, or anesthesia
o) Immediate family member with a known or suspected Familial Cancer Syndrome (including hereditary breast and ovarian cancer syndrome, hereditary non-polyposis colorectal cancer syndrome, and familial adenomatous polyposis)
p) Need for therapeutic anticoagulation treatment during the period of conditioning through platelet engraftment
q) Clinically significant pulmonary hypertension at baseline, as defined by the requirement for ongoing pharmacologic treatment or the consistent or intermittent use of supplemental home oxygen
r) Pregnancy or breastfeeding
s) History of a significant bleeding disorder

BSWHP considers only ONE treatment per lifetime medically necessary as repeat administration of lovotibeglogene autotemcel (Lyfgenia™) is experimental and investigational because the effectiveness of this strategy has not been established.

BSWHP considers lovotibeglogene autotemcel (Lyfgenia™) for the treatment of all other indications to be experimental and investigational because the effectiveness of this strategy has not been established.

All requests will be reviewed by a clinical pharmacist and medical director.

BACKGROUND:

Sickle Cell Disease (SCD) is a single-gene disorder in which 1 DNA base-pair alteration in the gene coding for hemoglobin produces sickle hemoglobin (HbS) when inherited in an autosomal recessive fashion with a second HbS or when combined with other hemoglobin variants (e.g., HbC or β-

thalassemia). When deoxygenated within capillary beds sickle hemoglobin forms long chains which distorts the red blood cell (RBC) into a sickle shape. Sickled RBCs have increased adhesion molecules compared to normal RBCs that facilitate binding to endothelial walls. In addition, Sickle cells hemolyze rapidly. Recurrent RBC sickling and hemolysis, combined with endovascular inflammation, result in acute and chronic organ damage at the cellular level, associated with acute, unpredictable, and potentially life-threatening complications.[1]

In the US, approximately 100,000 people have SCD. Children born in the US may be diagnosed shortly after birth through newborn screening programs. SCD is characterized by hemolytic anemia, acute and chronic pain, acute chest syndrome; increased incidence of stroke, nephropathy, and retinopathy; and a life span that is 20 years shorter than the general population.[1] A cure for SCD today is a stem cell transplant from a matched donor, but this option is only available to a small fraction of patients living with SCD because of the lack of available donors.[3]

Lovotibeglogene autotemcel (Lyfgenia™) is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of patients 12 years of age or older with sickle cell disease and a history or vaso-occlusive events.[2]

Lovotibeglogene is a $\beta^{A\text{-}T87Q}$-globin gene therapy consisting of autologous CD34+ cells from patients with sickle cell disease containing hematopoietic stem cells (HSCs) transduced with BB305 LVV encoding $\beta^{A\text{-}T87Q}$-globin, suspended in cryopreservation solution. Lovotibeglogene is intended for one-time administration to add functional copies of a modified form of the β-globin gene ($\beta^{A\text{-}T87Q}$-globin) into the patient's own HSC.[2]

Lovotibeglogene is prepared using the patient's own HSCs, which are collected via apheresis procedure(s). The autologous cells are enriched for CD34+ cells, then transduced ex vivo with BB305 LVV. The transduced CD34+ cells are washed, formulated into a suspension, and then cryopreserved. LYFGENIA is frozen in a patient-specific infusion bag(s) and is thawed prior to administration.[2]

After lovotibeglogene infusion, the transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce red blood cells containing biologically active $\beta^{A\text{-}T87Q}$–globin that will combine with α-globin to produce functional Hb containing $\beta^{A\text{-}T87Q}$–globin (HbA^{T87Q}).[2]

HbA^{T87Q} has similar oxygen-binding affinity and oxygen hemoglobin dissociation curve to wild type HbA, reduces intracellular and total hemoglobin S (HbS) levels, and is designed to sterically inhibit polymerization of HbS thereby limiting the sickling of red blood cells.[2]

The efficacy of lovotibeglogene was studied in a single-arm, 24-month, open-label, multicenter Phase 1/2 (NCT02140554, Study 1-C) and continued on a long-term follow-up study. In Study 1-C, 36 patients received the intravenous infusion of lovotibeglogene. Patients with a history of at least 4 VOEs in the 24 months prior to informed consent (n=32) were included in the VOE efficacy outcomes. The efficacy outcomes were complete resolution of Vaso-occlusive Events (VOE-CR) and severe VOEs (sVOE-CR) between 6 months and 18 months after infusion of lovotibeglogene.[2]

In HBG-206 Group C (n=32), 88% (95% CI) of patients experienced complete resolution of VOEs and 94% (95% CI) of patients experienced complete resolution of severe VOEs through 18 months post infusion with lovotibeglogene. [2]

The median (min, max) duration of follow-up for the patients in the study is 38 (12, 61) months post lovotibeglogene infusion. After the primary evaluation period to last follow-up, 4 of 32 patients who achieved VOE-CR experienced VOEs while maintaining globin response. After the primary evaluation period up to 24 months, 17 of 35 (49%) patients were prescribed opioids for sickle cell and non-sickle cell-related pain. [2]

CODES:

Important note: *Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.*

CPT Codes:	96413 - Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug	
HCPCS Codes:	J3394 – Injection, lovotibeglogene autotemcel, per treatment	
ICD10 codes:	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
ICD10 Not covered:		

POLICY HISTORY:

Status	Date	Action
New	06/10/2024	New Policy
Update	06/09/2025	Updated Medicaid language to align with standard language, Updated beginning note to align with standard language, Updated treatment center criteria to attestation only, Updated genotype criteria to include a diagnosis of Sickle Cell Disease, Added “any of the following” to the sVOE criteria, Updated one treatment per lifetime note, other indications note, and references note to align with standard language, Updated HCPCS code: J3590 to J3394, Updated ending note sections to align with business entity changes
Update	8/11/2025	Removed, Medicare NCD/LCD Interqual statement for clarity.

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and may modify it at a later date based upon the evolution of the published clinical evidence. Should additional scientific studies become available, and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

1. Kavanagh PL, Fasipe T, Wun T. Sickle cell disease. *JAMA*. 2022;328(1):57. doi:10.1001/jama.2022.10233

2. Food and Drug Administration. FDA label: Lyfgenia™ (lovotibeglogene autotemcel). Accessed April 16, 2025. https://www.fda.gov/media/xxx.pdf
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. doi:10.1056/NEJMoa2117175

***Note**:*
Health Maintenance Organization (HMO) products are offered through Scott and White Health Plan dba Baylor Scott & White Health Plan, and Scott & White Care Plans dba Baylor Scott & White Care Plan. Insured PPO and EPO products are offered through Baylor Scott & White Insurance Company. Scott and White Health Plan dba Baylor Scott & White Health Plan serves as a third-party administrator for self-funded employer-sponsored plans. Baylor Scott & White Care Plan and Baylor Scott & White Insurance Company are wholly owned subsidiaries of Scott and White Health Plan. These companies are referred to collectively in this document as Baylor Scott & White Health Plan.

RightCare STAR Medicaid is offered through Scott and White Health Plan in the Central Texas Medicaid Rural Service Area (MRSA); FirstCare STAR is offered through SHA LLC dba FirstCare Health Plans (FirstCare) in the Lubbock and West MRSAs; and FirstCare CHIP is offered through FirstCare in the Lubbock Service Area.