09-J4000-83

Original Effective Date: 04/01/24

Reviewed: 05/14/25

Revised: 06/15/25

Subject: Lovotibeglogene autotemcel (Lyfgenia) suspension for IV infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Sickle cell disease (SCD) represents a group of inherited disorders carried by the beta allele of the hemoglobin (Hb) gene. It is characterized by abnormal hemoglobin polymerization that results in a sickle-shaped erythrocyte. This sickled alteration results in a shortened lifespan of the erythrocyte (16 days vs 120 days in normal RBCs) and ultimately results in vascular occlusion. The term SCD includes the homozygous genotype HbSS and the heterozygous genotypes HbSβ0 thalassemia, HbSC, HbSD, and HbSβ+ thalassemia. An individual with one normal gene and one HbS gene (HbAS) is a carrier and referred to as “sickle cell trait”. Sickle cell trait typically does not have clinical manifestations of the disease. Acutely, patients with SCD present with recurrent pain episodes, life-threatening infections due to splenic infarction, acute chest syndrome, pulmonary hypertension, stroke, and cumulative multiorgan damage. These episodes are categorized as vaso-occlusive crises (VOCs). Treatment options for SCD include hydroxyurea, L-glutatmine, crizanlizumab, voxelotor, and blood transfusions. The only curative option is hematopoietic stem cell transplantation (HSCT).

On December 8, 2023, the FDA approved lovotibeglogene autotemcel (Lyfgenia) for the treatment of patients 12 years of age or older with sickle cell disease (SCD) and a history of vaso-occlusive events (VOE). Lovotibeglogene autotemcel (Lyfgenia) is a gene therapy consisting of autologous CD34+ cells from patients with sickle cell disease containing hematopoietic stem cells (HSCs) transduced with BB305 LVV encoding βA-T87Q-globin, suspended in cryopreservation solution. It is intended for one-time administration to add functional copies of the modified form of the β-globin gene (βA-T87Q-globin gene) into the patient’s own HSCs. After lovotibeglogene autotemcel (Lyfgenia) infusion, the transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce red blood cells containing biologically active βA-T87Q-globin that will combine with α-globin to produce functional Hb containing βA-T87Q-globin (HbAT87Q). HbAT87Q 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.

Based on the manufacturer prescribing information, the efficacy and safety of lovotibeglogene autotemcel (Lyfgenia) was evaluated in a single-arm, 24-month, open-label, multicenter Phase 1/2 study. A total of 43 patients underwent apheresis after mobilization with plerixafor of which 36 patients received myeloablative busulfan conditioning. Seven patients did not proceed to conditioning; 2 patients discontinued due to apheresis-related issues and 5 discontinued at patient and/or physician discretion. Thirty-six patients received the intravenous infusion of lovotibeglogene autotemcel (Lyfgenia) with a median dose of 6.4 (range: 3 - 14) × 106 CD34+ cells/kg 48 hours after the last dose of busulfan. No patients experienced graft failure or graft rejection. The transplant population for VOE efficacy outcomes included patients with a history of at least 4 VOEs in the 24 months prior to informed consent. The efficacy outcomes were complete resolution of VOEs and severe VOEs between 6 months and 18 months after the infusion. VOEs were defined as any of the following events requiring evaluation at a medical facility: an episode of acute pain with no medically determined cause other than vaso-occlusion, lasting more than 2 hours, acute chest syndrome, acute hepatic sequestration, acute splenic sequestration. Severe VOE were defined as either of the following events: VOE requiring a hospitalization or multiple visits to an emergency department/urgent care over 72 hours and receiving intravenous medications at each visit and priapism requiring any level of medical attention. The VOE outcomes are summarized in Table 1.

Table 1: VOE outcomes after lovotibeglogene autotemcel (Lyfgenia) infusion

Clinical Attribute	**Results**
Complete resolution of VOE	
n/N (%)	28/32 (88%)
[95% CI]	[71, 97]
Complete resolution of severe VOE	
n/N (%)	30/32 (94%)
[95% CI]	[79, 99]

Globin response (GR) was defined as meeting the following criteria for a continuous period of at least 6 months after lovotibeglogene autotemcel (Lyfgenia) infusion: weighted average hemoglobin AT87Q percentage of non-transfused total Hb greater than or equal to 30% and weighted average non-transfused total Hb (HbS+HbF+HbA2+HbAT87Q) increase of greater than or equal to 3 g/dL compared to baseline total Hb or weighted average non-transfused total Hb greater than or equal to 10 g/dL. All 36 patients infused in trial were evaluated for globin response, and 31/36 (86%) achieved GR. All patients maintained GR once it was achieved. The median duration of follow-up for these patients (N = 36) was 38 months (range: 12 - 61 months) post infusion. After the primary evaluation period to last follow-up, 4 of 32 patients who achieved complete resolution of VOE experienced VOEs while maintaining GR. 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.

As outline in the lovotibeglogene autotemcel (Lyfgenia) prescribing information, the most common adverse reactions equal to or greater than Grade 3 (incidence ≥ 20%) were stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia.

POSITION STATEMENT:

The administration of lovotibeglogene autotemcel (Lyfgenia) **meets the definition of medical necessity** when **ALL** of the following are met:

1. Member is at least 12 years of age at the time of treatment
2. Diagnosis of Sickle Cell Disease (e.g., genotypes βS/βS or βS/β0 or βS/β+) as determined by one of the following ("a" or "b"): - laboratory documentation must be submitted
    a. Identification of significant quantities of HbS with or without an additional abnormal β-globin chain variant by hemoglobin assay
    b. Identification of biallelic HBB pathogenic variants where at least one allele is the p.Glu6Val pathogenic variant on molecular genetic testing
3. Member does **NOT** have disease with more than two α-globin gene deletions
4. Two or more vaso-occlusive crises/events* in the previous 12 months (or four or more VOC/VOEs in the previous 24 months) that required a visit to a medical facility (e.g., hospital, ER) and intervention while receiving hydroxyurea and add-on therapy (e.g., crizanlizumab, voxelotor). If not on therapy, documentation of intolerance/contraindication must be provided. - laboratory or medical record documentation must be submitted
5. Member is clinically stable and able to undergo a hematopoietic stem cell transplant (HSCT) in the opinion of treating physician
6. Member does **NOT** have an available, suitable, and willing fully matched sibling human leukocyte antigen donor < 18 years old to participate in an allogeneic HSCT
7. Member has **NOT** previously received gene therapy (including lovotibeglogene autotemcel) **OR** an allogeneic HSCT in their lifetime
8. Member has a negative serologic test for HIV infection (i.e., the member is **NOT** HIV positive) - laboratory documentation within the last 6 months must be submitted
9. Member will be transfused at least twice (once each month) prior to mobilization to reach a target Hb of 8 to 10 g/dL (not to exceed 12 g/dL) and a HbS level less than 30%
10. Attestation that the following medications will **NOT** be administered:
    a. Iron chelators for 7-days prior to mobilization and conditioning and 6 months post-treatment for myelosuppressive iron chelators
    b. Hydroxyurea for at least 2 months prior to mobilization and until all cycles of apheresis are completed (Note: If hydroxyurea is administered between mobilization and conditioning, discontinue 2 days prior to initiation of conditioning)
    c. Other disease-modifying agents (e.g., L-glutamine, voxelotor, crizanlizumab) for at least 2 months prior to mobilization
    d. Granulocyte-colony stimulating factor (G-CSF) for mobilization of hematopoietic stem cells (HSC)
    e. Erythropoietin for at least 2 months prior to mobilization
    f. Prophylactic HIV anti-retroviral medication within 30 days (or earlier for long-acting agents) prior to stem cell mobilization and until all cycles of apheresis are completed.

11. Member does **NOT** have **ANY** of the following ("a" to "c"): - documentation within the last 6 months must be submitted
    a. Advanced liver disease defined as **ANY** of the following ("i" to "iv"):
        i. Persistent aspartate transaminase (AST), alanine transaminase (ALT), or direct bilirubin value greater than 3-times the upper limit of normal (ULN)
        ii. Baseline prothrombin time or partial thromboplastin time greater than 1.5-times the ULN
        iii. Imaging test (e.g., MRI, CT, ultrasound) of the liver demonstrating clear evidence of cirrhosis
        iv. Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis
    b. Baseline estimated glomerular filtration rate (eGFR) less than 70 mL/min/1.73 m^2
    c. Clinically significant and active bacterial, viral, fungal, or parasitic infection
12. Lovotibeglogene autotemcel will be administered at a Lyfgenia Qualified Treatment Center
13. The administration of lovotibeglogene autotemcel will not exceed one single dose as provided by the manufacturer

Approval duration: 9 months to allow for a one-time infusion of therapy

*Vaso-occlusive crises/events are defined as events requiring a visit to a medical facility (e.g., hospital, ER) AND necessitating intervention (e.g., opioid pain management, non-steroidal anti-inflammatory drugs, RBC transfusion, medical procedure) for one or more of the following: acute pain with no medically determined cause other than vaso-occlusion, acute chest syndrome, acute splenic sequestration, acute hepatic sequestration, and priapism lasting greater than 2 hours.

Lovotibeglogene autotemcel (Lyfgenia) is considered **experimental or investigational** for any other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcome.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- 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 (SCD) and a history of vaso-occlusive events.
- Lovotibeglogene autotemcel (Lyfgenia) has not been studied in patients with more than two α-globin gene deletions.

- Dosing of lovotibeglogene autotemcel (Lyfgenia) is based on the number of CD34+ cells in the infusion bag(s) per kg of body weight. The minimum recommended dose is 3 × 106 CD34+ cells/kg.
- Before mobilization, apheresis, and myeloablative conditioning are initiated, confirm that hematopoietic stem cell (HSC) transplantation is appropriate for the patient.
- Patients must be screen for HIV-1 and HIV-2 before collection of cells for manufacturing.
- Lovotibeglogene autotemcel (Lyfgenia) is an autologous HSC-based gene therapy that is prepared from the patient's HSCs, which are collected via apheresis procedures. Patients must undergo HSC mobilization and apheresis to obtain CD34+ cells for manufacturing. Single agent plerixafor is used for mobilization; G-CSF should not be administered for mobilization. Also anti-retroviral medications should not be taken within 30 days prior to stem cell mobilization and until all cycles of apheresis are complete; there are some long-acting anti-retroviral medications that may require a longer duration of discontinuation for elimination of the medication.
- Patients should be transfused at least twice (once each month) prior to mobilization to reach a target Hb of 8 to 10 g/dL (not to exceed 12 g/dL) and a HbS level less than 30%.
- Discontinue hydroxyurea for at least 2 months prior to mobilization and until all cycles of apheresis are completed.: If hydroxyurea is administered between mobilization and conditioning, discontinue 2 days prior to initiation of conditioning. Other disease-modifying agents (e.g., L-glutamine, voxelotor, crizanlizumab) should be discontinued for at least 2 months prior to mobilization.
- Stop iron chelators at least 7 days prior to mobilization and conditioning and avoid use of myelosuppressive iron chelators for 6 months post-treatment.
- Full myeloablative and lymphodepleting conditioning must be administered before infusion of lovotibeglogene autotemcel (Lyfgenia). Following myeloablative conditioning, allow a minimum of 48 hours of washout before lovotibeglogene autotemcel (Lyfgenia) infusion.
- Administration of lovotibeglogene autotemcel (Lyfgenia) occurs at participating sites. Prior to administration, one must verify the patient's identity matches the unique patient identification information on the metal cassette(s), infusion bag(s), and Lot Information Sheet.
- Keep the infusion bag(s) in the metal cassette(s) and store in the vapor phase of liquid nitrogen at less than or equal to -140°C (≤ -220°F) until ready for thaw and administration.
- Lovotibeglogene autotemcel (Lyfgenia) is a cell suspension for intravenous infusion. Administer each infusion bag of lovotibeglogene autotemcel (Lyfgenia) via intravenous infusion (drip) by gravity flow over a period of less than 30 minutes and no more than 4 hours after thawing, and when the dose consists of multiple bags, thaw and administer one bag at a time. Do not use an in-line blood filter or an infusion pump to administer lovotibeglogene autotemcel (Lyfgenia). Additionally, do not sample, alter, irradiate, or refreeze lovotibeglogene autotemcel (Lyfgenia).

Dose Adjustments

- Lovotibeglogene autotemcel (Lyfgenia) has not been studied in patients with renal impairment (i.e., GFR less than 70 mL/min/1.73 m^2) or hepatic impairment.

Drug Availability

- Lovotibeglogene autotemcel (Lyfgenia) is supplied in one to four infusion bags containing a frozen suspension of genetically modified autologous cells, enriched for CD34+ cells.

- Each bag contains approximately 20 mL. Each infusion bag is individually packed within an overwrap in a metal cassette (NDC 73554-1111-1).
- Lovotibeglogene autotemcel (Lyfgenia) is shipped from the manufacturing facility to the treatment center storage facility in a cryoshipper, which may contain multiple metal cassettes intended for a single patient. A Lot Information Sheet is affixed inside the shipper.

PRECAUTIONS:

Boxed Warning

- **Hematologic malignancy:** Hematologic malignancy has occurred in patients treated with lovotibeglogene autotemcel (Lyfgenia). At the time of initial product approval, two patients treated with an earlier version of lovotibeglogene autotemcel (Lyfgenia) using a different manufacturing process and transplant procedure developed acute myeloid leukemia (AML). One patient with α-thalassemia trait has been diagnosed with myelodysplastic syndrome (MDS). The additional hematopoietic stress associated with mobilization, conditioning, and infusion of lovotibeglogene autotemcel (Lyfgenia), including the need to regenerate the hematopoietic system, may increase the risk of a hematologic malignancy. Patients with sickle cell disease have an increased risk of hematologic malignancy as compared to the general population. Patients treated with lovotibeglogene autotemcel (Lyfgenia) may develop hematologic malignancies and should have lifelong monitoring. Monitor for hematologic malignancies with a complete blood count (with differential) at least every 6 months for at least 15 years after treatment with lovotibeglogene autotemcel (Lyfgenia), and integration site analysis at Months 6, 12, and as warranted.

Contraindications

- None

Precautions/Warnings

- **Delayed Platelet Engraftment:** Delayed platelet engraftment has been observed with lovotibeglogene autotemcel (Lyfgenia). Bleeding risk is increased prior to platelet engraftment and may continue after engraftment in patients with prolonged thrombocytopenia. Two patients (4%) required more than 100 days post treatment with lovotibeglogene autotemcel (Lyfgenia) to achieve platelet engraftment. Patients should be made aware of the risk of bleeding until platelet recovery has been achieved. Monitor patients for thrombocytopenia and bleeding according to standard guidelines. Conduct frequent platelet counts until platelet engraftment and platelet recovery are achieved. Perform blood cell count determination and other appropriate testing whenever clinical symptoms suggestive of bleeding arise.
- **Neutrophil Engraftment Failure:** There is a potential risk of neutrophil engraftment failure after treatment with lovotibeglogene autotemcel (Lyfgenia). Neutrophil engraftment failure is defined as failure to achieve three consecutive absolute neutrophil counts (ANC) ≥ 0.5 × 109 cells/L obtained on different days by Day 43 after infusion of lovotibeglogene autotemcel (Lyfgenia). Monitor neutrophil counts until engraftment has been achieved. If neutrophil engraftment failure occurs in a patient treated with lovotibeglogene autotemcel (Lyfgenia), provide rescue treatment with the back-up collection of CD34+ cells.

- **Insertional Oncogenesis:** There is a potential risk of lentiviral vector-mediated insertional oncogenesis after treatment with lovotibeglogene autotemcel (Lyfgenia).
- **Hypersensitivity Reactions:** Allergic reactions may occur with the infusion of lovotibeglogene autotemcel (Lyfgenia). The dimethyl sulfoxide (DMSO) or dextran 40 in lovotibeglogene autotemcel (Lyfgenia) may cause hypersensitivity reactions, including anaphylaxis.
- **Anti-retroviral Use:** Patients should not take prophylactic HIV anti-retroviral medications for at least one month prior to mobilization and until all cycles of apheresis are completed. There are some long-acting anti-retroviral medications that may require a longer duration of discontinuation for elimination of the medication. If a patient is taking anti-retrovirals for HIV prophylaxis, confirm a negative test for HIV before beginning mobilization and apheresis of CD34+ cells.
- **Hydroxyurea Use:** Patients should not take hydroxyurea for at least 2 months prior to mobilization and until all cycles of apheresis are completed. If hydroxyurea is administered between mobilization and conditioning, discontinue 2 days prior to initiation of conditioning.
- **Iron Chelation:** Do not administer myelosuppressive iron chelators for 6 months post-treatment with lovotibeglogene autotemcel (Lyfgenia).
- **Interference with PCR-based Testing:** Patients who have received lovotibeglogene autotemcel (Lyfgenia) are likely to test positive by polymerase chain reaction (PCR) assays for HIV due to integrated BB305 LVV proviral DNA, resulting in a possible false-positive PCR assay test result for HIV. Therefore, patients who have received lovotibeglogene autotemcel (Lyfgenia) should not be screened for HIV infection using a PCR-based assay.

BILLING/CODING INFORMATION:

HCPCS Coding

J3394	Injection, lovotibeglogene autotemcel, per treatment

ICD-10 Diagnosis Codes That Support Medical Necessity

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
D57.04	Hb-SS disease with dactylitis
D57.09	Hb-SS disease with crisis with other specified complication
D57.211	Sickle cell/Hb-C disease with acute chest syndrome
D57.212	Sickle cell/Hb-C disease with splenic sequestration
D57.214	Sickle-cell/Hb-C disease with dactylitis
D57.219	Sickle cell/Hb-C disease with crisis, unspecified
D57.411	Sickle cell thalassemia with acute chest syndrome
D57.412	Sickle cell thalassemia with splenic sequestration
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 with crisis, unspecified
D57.434	Sickle-cell thalassemia beta zero with dactylitis
D57.454	Sickle-cell thalassemia beta plus with dactylitis

D57.811	Other sickle cell disorders with acute chest syndrome
D57.812	Other sickle cell disorders with splenic sequestration
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

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Gene therapy - Gene therapies treat diseases by modifying or manipulating the expression of a gene or altering the properties of living cells for therapeutic use including: (1) replacing a disease-causing gene with a healthy copy of the gene, (2) inactivating a disease-causing gene that is not functioning properly, or (3) introducing a new or modified gene into the body to help treat a disease.

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2025. URL www.clinicalpharmacilogy-ip.com Accessed 02/24/25.
2. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2024. URL http://www.dynamed.com. Accessed 02/29/24.

3. Lyfgenia (lovotibeglogene autotemcel) [package insert]. Bluebird Bio, Inc. Somerville (MA): December 2023.
4. Micromedex Healthcare Series [Internet Database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically. Accessed 02/24/25.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 05/14/25.

GUIDELINE UPDATE INFORMATION:

04/01/24	New Medical Coverage Guideline – Lovotibeglogene autotemcel (Lyfgenia) indicated for the treatment of patients aged 12 years and older with genetically confirmed sickle cell disease with recurrent vaso-occlusive crises/events who are clinically stable and able to undergo a HSCT but do not have a HLA-matched willing family donor.
07/01/24	Revision: Added HCPCS code J3394 and deleted code J3590.
04/15/25	Review and revision of guideline consisting of updating references and billing codes.
06/15/25	Review and revision of guideline consisting of revising the position statement to list examples of genotypes, allowing VOC/VOEs to present to a medical facility such as an ER, defining frequency of VOC/VOEs to be 2 or more in the previous 12 months or 4 or more in the previous 24 months, limiting the HLA-matched family donor requirement to members less than 18 years old, removing cell count requirements, clarifying imaging tests such as MRI, ultrasound and CT for assessment of liver disease, outlining the types of active infections, and requesting lab and imaging documentation to be within the last 6 months.