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**P&T Date: 06/05/2025**

### **Lyfgenia™ (lovotibeglogene autotemcel)**

**HCPCS: J3394**

#### **Policy:**

*Requests must be supported by submission of chart notes and patient specific documentation.*

- A. Coverage of the requested drug is provided when all the following are met:
  - a. FDA approved indication
  - b. FDA approved age
  - c. Prescribing by or in consultation with a hematologist
  - d. Diagnosis of sickle cell disease (SCD) confirmed via genetic testing or electrophoresis
  - e. Must not be diagnosed with sickle  $\beta$ -thalassemia
  - f. Must have experienced at least 4 severe vaso-occlusive crises in the past 24 months
  - g. Trial and failure, contraindication, or intolerance to hydroxyurea
  - h. Must not have any of the following:
    - i. Positive presence of HIV-1 or HIV-2, hepatitis B, or hepatitis C
    - ii. Inadequate bone marrow function, as defined by an absolute neutrophil count of less than 1000/ $\mu$ L or less than 500/ $\mu$ L for patient taking hydroxyurea or a platelet count less than 120,000/ $\mu$ L without hypersplenism
    - iii. Advanced liver disease defined as AST, ALT, or total bilirubin greater than 3 times the upper limit of normal
    - iv. Prior treatment with an allogenic stem cell transplant
    - v. Prior or current malignancy or immunodeficiency disorder
  - i. Must not have received prior treatment with any gene therapy for sickle cell disease or are being considered for treatment with any other gene therapy for sickle cell disease
  - j. The requesting physician attests to providing clinical outcome information within the appropriate provider portal as requested by BCBSM
  - k. Trial and failure, intolerance, or a contraindication to the preferred products as specified in the BCBSM/BCN medical utilization management drug list
- B. Quantity Limitations, Authorization Period and Renewal Criteria
  - a. Quantity Limits: Align with FDA recommended dosing
  - b. Authorization Period: 12 months with the allowance of only one dose per lifetime
  - c. Renewal Criteria: Not applicable as no further authorization will be provided

This policy and any information contained herein is the property of Blue Cross Blue Shield of Michigan and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and BCBSM employees for the purpose of coverage determinations.

\*\*\*Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at <http://www.cms.hhs.gov/>. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

## Background Information:

- 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 (VOEs). Lyfgenia's use is limited in those with  $\alpha$ -thalassemia trait ( $-\alpha 3.7/-\alpha 3.7$ ) and they may experience anemia with erythroid dysplasia that may require chronic red blood cell transfusions. Lyfgenia has not been studied in patients with more than two  $\alpha$ -globin gene deletions.
- Sickle cell disease is a recessive hemolytic anemia caused by a mutation in the  $\beta$ -globin gene. It is characterized by the formation of sickle hemoglobin (HbS). HbS is less soluble and less elastic than fetal hemoglobin (HbF) or normal adult hemoglobin (HbA). The disease involves multicellular adhesion between sickled red blood cells, white blood cells, platelets, and endothelial cells resulting in vaso-occlusive crises (VOCs). VOCs are the hallmark of SCD and are experienced by approximately 70% of patients. They are recurring, unpredictable, painful events that decrease organ function with complications including stroke, pneumonia, vision loss, pulmonary hypertension, leg ulcers, and sepsis. VOCs are often treated as an emergency requiring acute care and are the number one reason patients with SCD visit the emergency room or are hospitalized.
- Hydroxyurea is a ribonucleotide reductase inhibitor which increases the amount of circulating HbF in the body and has been a mainstay of therapy. It also has been shown to lower the number of circulating leukocytes and reticulocytes altering the expression of adhesion molecules; raise red blood cell (RBC) volume; and improve cellular deformability and rheology, all of which contribute to a decrease in VOCs. The 2014 National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease Guidelines recommend the use of hydroxyurea for the following patient populations:
  - In adults with SCD who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period
  - In adults with SCD who have sickle cell-associated pain that interferes with daily activities and quality of life
  - In adults with SCD who have a history of severe and/or recurrent acute coronary syndrome
  - In adults with SCD who have severe symptomatic chronic anemia that interferes with daily activities or quality of life
  - In infants 9 months of age and older, children, and adolescents with SCD, offer treatment with hydroxyurea regardless of clinical severity to reduce complications
  - In adults and children with SCD who have chronic kidney disease and are taking erythropoietin
- The guidelines recommend starting hydroxyurea at a dose of 15 mg/kg/day for adults and increasing the dose by 5 mg/kg/day every 8 weeks to a maximum dose of 35 mg/kg/day. A clinical response to therapy may take 3 – 6 months. Therefore, a 6 month trial on the maximum tolerated dose is required prior to considering discontinuation

due to treatment failure, whether due to lack of adherence or failure to respond to therapy. Guidelines have not yet been updated to include recommendations for use of gene therapy.

- Safety and efficacy were evaluated in the HGB-206 trial, a single-arm, 24-month, open-label, multicenter Phase I/II study of 32 patients with SCD and a history of at least 4 VOs in the 24 months prior to study entry. Subjects were excluded from the trial if they had sickle  $\beta$ -thalassemia; were positive for HIV-1 or HIV-2, hepatitis B, or hepatitis C; had inadequate bone marrow function, as defined by an absolute neutrophil count of less than 1000/ $\mu$ L or less than 500/ $\mu$ L for patient taking hydroxyurea or a platelet count less than 120,000/ $\mu$ L without hypersplenism; had advanced liver disease defined as AST, ALT, or total bilirubin greater than 3 times the upper limit of normal; had prior treatment with an allogeneic stem cell transplant; or had a prior or current malignancy or immunodeficiency disorder. The primary endpoints were complete resolution of VOs (VOE-CR) and severe VOs (sVOE-CR) between 6 months and 18 months after infusion of Lyfgenia. VOs 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 (ACS); acute hepatic sequestration; and/or acute splenic sequestration. Severe VOE (sVOE) 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 or priapism requiring any level of medical attention. Twenty-eight (88%) of 32 patients achieved VOE-CR between 6 and 18 months after Lyfgenia infusion. Thirty (94%) of 32 patients achieved sVOE-CR during the 6 and 18 months after infusion of Lyfgenia.
- There is currently no data supporting administration of Lyfgenia following administration of another gene therapy. Lyfgenia should not be given following any other gene therapy for SCD as safety and efficacy has not been established.

## References:

1. Lyfgenia [prescribing information]. Somerville, MA: Bluebird Bio, Inc.; December 2023.
2. Centers for Disease Control and Prevention. Sickle cell disease: data and statistics. 2023 July 6. Available at: <https://www.cdc.gov/ncbddd/sicklecell/data.html>. Accessed on: December 11, 2023.
3. Ogedegbe HO. Sickle cell disease: an overview. *Laboratory Medicine*. 2002; 33(7): 515 – 543.
4. Centers for Disease Control and Prevention. Sickle cell disease: complications and treatments. 2023 July 6. Available at: <https://www.cdc.gov/ncbddd/sicklecell/treatments.html>. Accessed on December 11, 2023.
5. Brousseau DC, Panepinto JA, Nimmer M, et al. The number of people with sickle-cell disease in the United States: national and state estimates. *Am J Hematol*. 2010; 85(1): 77 – 78.
6. National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease: expert panel report, 2014. Available at: <https://www.nhlbi.nih.gov/sites/default/files/publications/56-364NFULL.pdf>. Accessed on: December 11, 2023.
7. Negre O, Eggimann AV, Beuzard Y, et al. Gene therapy of the  $\beta$ -hemoglobinopathies by lentiviral transfer of the  $\beta$ (A(T87Q))-globulin gene. *Hum Gene Ther*. 2016; 27 (2): 148–165.
8. Clinicaltrials.gov. A study evaluating the efficacy and safety of lentiGlobin BB305 drug product in beta-thalassemia major and sickle cell disease (NCT02151526). Available at: <https://clinicaltrials.gov/ct2/show/NCT02151526?term=lentiglobin&cond=Beta-Thalassemia&draw=1&rank=4>. Accessed on December 11, 2023.
9. Clinicaltrials.gov. A study evaluating the safety and efficacy of the lentiGlobin BB305 drug product in severe sickle cell disease (NCT02140554). Available at: <https://clinicaltrials.gov/ct2/show/NCT02140554?intr=%22LentiGlobin+BB305%22+OR+%22Zynteglo%22&draw=2&rank=5>. Accessed on December 11, 2023.

Policy History												
#	Date	Change Description										
1.5	P&T Date: 06/05/2025  Effective Date: 07/21/2025	Updated to include the required use of a provider portal to submit clinical outcomes data after Lyfgenia administration										
1.4	Effective Date: 12/12/2024	Updated to allow use of electrophoresis for diagnosis of sickle cell disease and changed the authorization period from 6 months to 12 months										
1.3	Effective Date: 02/08/2024	New policy - replaces previously approved preliminary criteria										
1.2	Effective Date: 01/02/2024	UM medical management system update for BCNA and MAPPO <table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	Yes	BCNA	Yes
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1.0	Effective Date: 10/12/2023	Preliminary Drug Review <table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>No</td></tr><tr><td>BCN</td><td>No</td></tr><tr><td>MAPPO</td><td>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	No	BCN	No	MAPPO	No	BCNA	No
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\* The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or <http://dailymed.nlm.nih.gov/dailymed/index.cfm>.