Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

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 β-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/µL or less than 500/µL for patient taking hydroxyurea or a platelet count less than 120,000/µL 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

***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 α-thalassemia trait (-α3.7/-α3.7) 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 α-globin gene deletions.

- Sickle cell disease is a recessive hemolytic anemia caused by a mutation in the β-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 VOEs in the 24 months prior to study entry. Subjects were excluded from the trial if they had sickle β-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/µL or less than 500/µL for patient taking hydroxyurea or a platelet count less than 120,000/µL 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 allogenic stem cell transplant; or had a prior or current malignancy or immunodeficiency disorder. The primary endpoints were complete resolution of VOEs (VOE-CR) and severe VOEs (sVOE-CR) between 6 months and 18 months after infusion of Lyfgenia. 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 (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 β-hemoglobinopathies by lentiviral transfer of the β(A(T87Q))-globulin gene. Hum Gene Ther. 2016; 27 (2): 148–165.
8. Clinicaltrial.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.

<table>
<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.5</td><td>P&T Date:
06/05/2025

Effective Date:
07/21/2025</td><td>Updated to include the required use of a provider portal to submit clinical outcomes data after Lyfgenia administration</td></tr>
<tr><td>1.4</td><td>Effective Date:
12/12/2024</td><td>Updated to allow use of electrophoresis for diagnosis of sickle cell disease and changed the authorization period from 6 months to 12 months</td></tr>
<tr><td>1.3</td><td>Effective Date:
02/08/2024</td><td>New policy - replaces previously approved preliminary criteria</td></tr>
<tr><td>1.2</td><td>Effective Date:
01/02/2024</td><td>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></td></tr>
<tr><td>1.1</td><td>Effective Date:
12/21/2023</td><td>UM medical management system update for BCN and BCBS
<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>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table></td></tr>
<tr><td>1.0</td><td>Effective Date:
10/12/2023</td><td>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></td></tr>
</table>

** 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.*

Blue Cross Blue Shield/Blue Care Network of Michigan
Medication Authorization Request Form
Lyfgenia™ (lovotibeglogene autotemce)
HCPCS CODE: J3394

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

This form is to be used by participating physicians to obtain coverage for Lyfgenia. For commercial members only, please complete this form and submit via fax to 1-877-325-5979. If you have any questions regarding this process, please contact BCBSM Provider Relations and Servicing or the Medical Drug Helpdesk at 1-800-437-3803 for assistance.

PATIENT INFORMATION		PHYSICIAN INFORMATION
Name		**Name**
ID Number		**Specialty**
D.O.B.	☐Male ☐Female	**Address**
Diagnosis		**City /State/Zip**
Drug Name	☐ Lyfgenia	**Phone/Fax: P**: ( ) - **F**: ( ) -
Dose and Quantity		**NPI**
Directions		**Contact Person**
Date of Service(s)		**Contact Person Phone / Ext.**

STEP 1: DISEASE STATE INFORMATION

1. Is this request for: ☐ Initiation ☐ Continuation of therapy *Date when patient started therapy:* _____
2. Please provide the NPI number for the place of administration: _____
3. Please specify the location of administration (e.g. name of facility): _____

4. **Initiation AND Continuation of therapy:**
   a. What is the patient's diagnosis?
      ☐ Sickle cell disease (SCD)
      ☐ β-thalassemia
      ☐ Other – *please specify diagnosis:* _____

   b. Does the patient have a genetic test confirming sickle cell disease? ***(Please attach any tests confirming diagnosis)***
      ☐ Yes ☐ No

   c. How many vaso-occlusive crises has the patient experienced in the past 24 months? ☐ <4 ☐ ≤4

   d. Has the patient tried and failed or has a contraindication or intolerance to hydroxyurea?
      ☐ Yes ☐ No, please explain: _____

   e. Has the patient received or being considered for any other gene therapy treatments?
      ☐ Yes, please explain: _____ ☐ No

   f. Does the patient have any of the following:
      ☐ Positive presence of HIV-1 or HIV-2, hepatitis B, or hepatitis C
      ☐ Inadequate bone marrow function, as defined by an absolute neutrophil count of less than 1000/µL or less than 500/µL for patient taking hydroxyurea or a platelet count less than 120,000/µL without hypersplenism
      ☐ Prior treatment with an allogenic stem cell transplant
      ☐ Prior or current malignancy or immunodeficiency disorder
      ☐ Advanced liver disease defined as alanine transferase greater than 3 times the upper limit of normal, total bilirubin greater than 2 times the upper limit of normal, or baseline prothrombin time 1.5 times the upper limit of normal
      ☐ Other: _____
      ☐ None of the above

   g. Has the patient received prior or being considered to receive gene therapy treatments for sickle cell disease?
      ☐ Yes, please explain: _____ ☐ No

5. Has the patient has experienced an intolerance, contraindication, or adverse event for the requested indication to Casgevy? Please provide date and type of intolerance patient has had. ☐ Yes, please explain: _____ ☐ No

6. **Continuation of therapy -** *Please include rationale for continuation of therapy*_____

7. *Please add any other supporting medical information necessary for our review*

Coverage will not be provided if the prescribing physician's signature and date are not reflected on this document.

☐ Request for expedited review: I certify that applying the standard review time frame may seriously jeopardize the life or health of the member or the member's ability to regain maximum function

Physician's Name **Physician Signature** **Date**

Step 2: Checklist	☐ Form Completely Filled Out ☐ Attached necessary chart notes	☐ Important laboratory results
Step 3: Submit	**By Fax: BCBSM Specialty Pharmacy Mailbox** **1-877-325-5979**	**By Mail: BCBSM Specialty Pharmacy Program** **P.O. Box 312320, Detroit, MI 48231-2320**