lovotibeglogene autotemcel (Lyfgenia®)

Policy # 00881
Original Effective Date: 07/01/2024
Current Effective Date: 07/01/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: exagamglogene autotemcel (Casgevy™) is addressed separately in medical policy 00880.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of lovotibeglogene autotemcel (Lyfgenia®)‡ for the treatment of sickle cell disease to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for lovotibeglogene autotemcel (Lyfgenia) will be considered when the following criteria are met:

- Patient is at least 12 years of age; AND
- Provider attests to consideration of the use of prophylaxis therapy for seizures prior to initiating myeloablative conditioning; AND
- Patient will be monitored for hematologic malignancies periodically after treatment; AND
- Lyfgenia will not be administered concurrently with live vaccines while the patient is immunosuppressed; AND
- Patient does not have a history of hypersensitivity to dimethyl sulfoxide (DMSO) or dextran 40; AND
- Patient is human immunodeficiency virus (HIV) negative as confirmed by a negative HIV test prior to mobilization; AND
  Note: Patients who have received 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 Lyfgenia should not be screened for HIV infection using a PCR-based assay);

- Patient will not receive therapy concomitantly with any of the following:
  - 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; AND
  - Myelosuppressive iron chelators (e.g., deferiprone, etc.) for 7 days prior to mobilization, conditioning, and 6 months post-treatment; AND
  - Disease-modifying agents (e.g., L-glutamine, voxelotor, crizanlizumab) for at least 2 months prior to mobilization; AND
  - Prophylactic HIV anti-retroviral therapy for at least one month prior to mobilization and until all cycles of apheresis are completed; AND
  - Mobilization of stem cells using granulocyte-colony stimulating factor (G-CSF); AND
  - Erythropoietin for at least 2 months prior to mobilization; AND
- Patient has not received other gene therapy [e.g., exagamglogene autotemcel (Casgevy®)‡]; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient is a candidate for autologous hematopoietic stem cell transplant (HSCT) and has not had prior autologous or allogeneic HSCT; AND
  *(Note: The part of this patient selection criterion requiring the patient to not have a prior HSCT is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- For patients under 18 years of age, the patient does not have a known and suitable 10/10 human leukocyte antigen (HLA) matched related donor willing to participate in an allogeneic HSCT; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility based on clinical trial data and will be denied as not medically necessary** if not met.)*
- Patient will be transfused at least twice (once each month) prior to mobilization to reach a target Hb of 8-10 g/dL (less than 12 g/dL) and < 30% HbS; AND

- Patient has a confirmed diagnosis of sickle-cell disease with one of the following genotypes βS/βS or βS/β0 or βS/β+ (Note: Additional genotypes will be considered on a case-by-case basis based on disease severity) as determined by one of the following:
    - Identification of significant quantities of HbS with or without an additional abnormal β-globin chain variant by hemoglobin assay; OR
    - Identification of biallelic *HBB* pathogenic variants where at least one allele is the p.Glu6Val pathogenic variant on molecular genetic testing; AND
- Patient does NOT have disease with more than two α -globin gene deletions; AND
- Patient has symptomatic disease despite treatment with hydroxyurea at any point in the past OR add-on therapy (e.g., crizanlizumab, voxelotor, etc.) OR has experienced intolerance; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient experienced two or more vaso-occlusive events/crises (defined as acute episodes of pain requiring a medical facility visit and treatment with oral or parenteral narcotic agents or a parenteral non-steroidal anti-inflammatory drug [NSAID]) in the previous year.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers lovotibeglogene autotemcel (Lyfgenia) when the patient has received other gene therapies or HSCT, when the patient does not have symptomatic disease despite treatment with or intolerance to a disease modifying agent, or when the patient is under 18 years of age and has a known and suitable HLA matched donor willing to participate in an allogeneic HSCT to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers lovotibeglogene autotemcel (Lyfgenia) when the patient selection criteria are not met (except those denoted above to be **not medically necessary****) to be **investigational.***

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Background/Overview

Lyfgenia is an autologous hematopoietic stem cell (HSC)-based gene therapy indicated for the treatment of sickle cell disease in patients ≥ 12 years of age with a history of vaso-occlusive crises/events (VOCs/VOEs). Treatment with Lyfgenia involves removal of a patient's CD34+ hematopoietic stem cells which are modified using a lentiviral vector to include a modified β-globin gene. After Lyfgenia infusion, the transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce red blood cells (RBCs) containing biologically active $\beta^{A\text{-}T87Q}$-globin that will combine with α-globin to produce functional hemoglobin, HbA^{T87Q}. This modified adult hemoglobin (HbA) inhibits polymerization of the sickle hemoglobin (HbS). The treatment process with Lyfgenia is long and complex and can take more than 6 months. First, HSCs of the patient are collected via mobilization and apheresis procedures. Then, the collected CD34+ cells are sent for manufacturing and quality control which takes approximately 10 to 15 weeks. After Lyfgenia is manufactured, the patient undergoes myeloablative conditioning with busulfan before receiving Lyfgenia by intravenous infusion. After the infusion, the patient is monitored for platelet and neutrophil engraftment. The product contains a boxed warning regarding the risk of hematologic malignancy. At the time of the initial product approval, two patients treated with an earlier version of Lyfgenia using a different manufacturing process and transplant procedure developed acute myeloid leukemia and one patient with an α-thalassemia trait was diagnosed with myelodysplastic syndrome. Patients should be monitored for evidence of malignancy through complete blood counts at least once every 6 months and through integration site analysis at Months 6, 12, and as warranted.

Sickle Cell Disease

Sickle cell disease is a group of inherited red blood cell disorders in which the hemoglobin is abnormal and leads to "sickling" of the red blood cells. This reduces the ability of the blood to transport oxygen to the body and can result in blocked blood vessels and tissue ischemia which manifest as various complications. Complications of sickle cell disease include acute vaso-occlusive crises/events (VOCs/VOEs) such as acute pain crises, splenic sequestration, acute chest syndrome, stroke, retinal damage, priapism, joint problems, and others. Patients with sickle cell disease have a shorter life expectancy than race-matched peers and often have a low quality of life due to frequent crises. Current pharmacologic treatment options for sickle cell disease include hydroxyurea (Droxia®, Siklos®, Hydrea®)‡, L-glutamine (Endari™)‡, crizanlizumab (Adakveo®)‡, and voxelotor (Oxbryta™)‡. Additionally, Lyfgenia and another gene therapy, Casgevy, are now approved for treatment of patients with sickle cell disease and recurrent VOCs. The most recent National Institutes

of Health-National Heart, Lung, and Blood Institute Evidence-based management of sickle cell disease guidelines were published in 2014 and do not include Endari, Adakveo, Oxbryta, Casgevy, or Lyfgenia. These guidelines note that only hydroxyurea and chronic blood transfusions are proven to be disease-modifying treatments for this condition. They recommend hydroxyurea therapy in most adult sickle cell disease patients as well as all pediatric patients ≥ 9 months of age.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Lyfgenia is approved for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Lyfgenia was studied in a single-arm, 24-month, open-label, multicenter Phase 1/2 study and continued in a long-term follow-up study. In the initial study, 43 subjects 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 Lyfgenia with a median (min, max) dose of 6.4 (3, 14) x 10^6 CD34+ cells/kg (48 hours after the last dose of busulfan). As Lyfgenia is an autologous therapy, prophylactic long-term immunosuppressive agents were not required in clinical studies. 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 (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
- Acute hepatic sequestration
- 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
- Priapism requiring any level of medical attention.

Of the 32 evaluated patients, 28 (88%) experienced VOE-CR (95% CI: 71, 97) and 30 (94%) experienced sVOE-CR (95% CI: 79, 99).

Globin response (GR) was defined as meeting the following criteria for a continuous period of at least 6 months after drug product infusion:

- Weighted average hemoglobin A^{T86Q} percentage of non-transfused total Hb $\geq$ 30% AND
- Weighted average non-transfused total Hb (HbS + HbF+ HbA_2+ HbA^{T87Q}) increase of $\geq$ 3 g/dL compared to baseline total Hb OR weighted average non-transfused total Hb $\geq$ 10 g/dL.

All 36 patients infused with Lyfgenia were evaluated for globin response with 31 (86%) achieving GR. All patients maintained GR once achieved.

The median (min, max) duration of follow-up for the patients in the study is 38 (12, 61) months post Lyfgenia infusion. After the primary evaluation period to last follow-up, 4 of the 32 patients who achieved VOE-CR 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.

Five patients with history of stroke or vasculopathy were treated in the study. All were at least 18 years old and on chronic transfusion therapy prior to Lyfgenia infusion. At 44-60 months follow up, all five subjects remain transfusion independent without recurrent stroke.

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References

1. Lyfgenia [package insert]. Bluebird bio, Inc. Somerville, MA. Updated January 2024.
2. Lyfgenia Drug Evaluation. Express Scripts. Updated December 2023.
3. The National Institutes of Health—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/media/docs/sickle-cell-diseasereport%20020816_0.pdf.

Policy History

Original Effective Date: 07/01/2024
Current Effective Date: 07/01/2024
06/06/2024 Medical Policy Committee review
06/12/2024 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 06/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy

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Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J3394
ICD-10 Diagnosis	D57.00-D57.819

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.