Clinical Policy: Lovotibeglogene Autotemcel (Lyfgenia)

Reference Number: CP.PHAR.627
Effective Date: 12.08.23
Last Review Date: 02.25
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Lovotibeglogene autotemcel (Lyfgenia®) is an autologous hematopoietic stem cell-based gene therapy.

FDA Approved Indication(s)

Lyfgenia is 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).

Limitation(s) of use: Following treatment with Lyfgenia, patients with α-thalassemia trait (-α3.7/- α3.7) 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.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

All requests reviewed under this policy **require medical director review**.

It is the policy of health plans affiliated with Centene Corporation® that Lyfgenia is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Sickle Cell Disease (must meet all)**:**

1. Diagnosis of SCD with genetic confirmation of β^s/β^s genotype (*see Appendix D*);
2. Prescribed by or in consultation with a hematologist and transplant specialist;
3. Age ≥ 12 years;
4. Documentation of ≥ 4 severe VOEs within the past 24 months, with a severe VOE defined as one of the following (a or b):
   a. Member experienced one of the following that required a hospitalization or multiple visits to an emergency department/urgent care over 72 hours and received intravenous medications at each visit (i, ii, iii, or iv):
      i. An episode of acute pain lasting > 2 hours with no medically determined cause other than vaso-occlusion;
      ii. Acute chest syndrome (ACS);
      iii. Acute hepatic sequestration;
      iv. Acute splenic sequestration;

b. Priapism requiring any level of medical attention;

5. Failure of hydroxyurea at up to the maximally indicated dose for ≥ 6 months, unless contraindicated or clinically significant adverse effects are experienced* (*see Appendix D*);
   **Myelosuppression and hydroxyurea treatment failure: Myelosuppression is dose-dependent and reversible and does not qualify for treatment failure. NHLBI guidelines recommend a 6 month trial on the maximum tolerated dose prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy. A lack of increase in mean corpuscular volume (MCV) and/or fetal hemoglobin (HbF) levels is not indication to discontinue therapy.*
6. Attestation from transplant specialist for both of the following (a and b):
   a. Member understands the risk and benefits of alternative therapeutic options such as allogeneic hematopoietic stem cell transplantation (HSCT);
   b. Member is clinically stable and eligible to undergo myeloablative conditioning and HSCT;
7. Member has not received prior allogeneic HSCT;
8. Member has not received prior gene therapy;
9. Member does not have ≥ 2 α-globin gene deletions (i.e., alpha-thalassemia trait);
10. Documentation from within the last 6 months that the member is negative for the presence of the following active infections: HIV, hepatitis B virus, and hepatitis C virus;
11. Member does not have advanced liver disease (*see Appendix E*);
12. Member does not have current malignancy or immunodeficiency disorder;
13. Documentation of member's body weight in kg;
14. Dose contains a minimum of 3×10^6 CD34+ cells/kg.

Approval duration: 6 months (one-time infusion per lifetime)

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Sickle Cell Disease

1. Continued therapy will not be authorized as Lyfgenia is indicated to be dosed one time only.

Approval duration: Not applicable

B. Other diagnoses/indications (must meet 1 or 2):

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ACS: acute chest syndrome
ANC: absolute neutrophil count
CBC: complete blood count
FDA: Food and Drug Administration
HbF: fetal hemoglobin
HIV: human immunodeficiency virus
HSCT: hematopoietic stem cell transplantation
MCV: mean corpuscular volume
NHLBI: National Heart, Lung, and Blood Institute
SCD: sickle cell disease
ULN: upper limit of normal
VOE: vaso-occlusive event
WBC: white blood cell

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
hydroxyurea‡	*Age ≥ 18 years* Initial: 15 mg/kg/dose PO once daily, rounded to the nearest 500-mg increment* *Age 9 months to 17 years* Initial: 20 mg/kg/dose PO once daily* ** Increase by 5 mg/kg/day every 8 weeks until mild myelosuppression (ANC 2,000 to 4,000/microliter) achieved.*	35 mg/kg/day
Droxia® (hydroxyurea)	*Age ≥ 18 years* Initial: 15 mg/kg/day PO single dose; based on blood counts, may increase by 5 mg/kg/day every 12 weeks to a max 35 mg/kg/day	
Siklos® (hydroxyurea)	*Age ≥ 18 years* Initial: 15 mg/kg PO QD* *Age 2 years to 17 years* Initial: 20 mg/kg PO QD* **Based on blood counts, may increase by 5 mg/kg/day every 8 weeks or if a painful crisis occurs*	

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
‡ *Off-label, 2014 NHLBI SCD guideline-supported dosing regimen*

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s): none reported
- Boxed warning(s): hematologic malignancy

Appendix D: General Information
- The eligibility criteria related to beta hemoglobin genotype for the pivotal HGB-206 Group C clinical trial included β^S/β^S, β^S/β^0, or β^S/β^+. However, upon enrollment and endpoint analysis, all study participants had confirmed β^S/β^S genotype. No study participants in the pivotal trial had the β^S/β^0 or β^S/β^+ genotype. Therefore, a confirmed β^S/β^S genotype is one of the criteria for Lyfgenia coverage to reflect the final study population evaluated in the clinical trial.
- Hydroxyurea dose titration: Members should obtain complete blood counts (CBC) with white blood cell (WBC) differential and reticulocyte counts at least every 4 weeks for titration. The following lab values indicate that it is safe to increase dose.
  - Absolute neutrophil count (ANC) in adults ≥ 2,000/µL, or ANC ≥ 1,250/µL in younger patients with lower baseline counts

- Platelet count ≥ 80,000/µL

If neutropenia or thrombocytopenia occurs: hydroxyurea dosing is held, CBC and WBC differential are monitored weekly, and members can restart hydroxyurea when values have recovered.

Appendix E: Advanced Liver Disease

- Examples of advanced liver disease include, but are not limited to, the following:
  - Cirrhosis
  - Bridging or significant fibrosis
  - Active hepatitis
  - Persistent aspartate transaminase, alanine transaminase, or direct bilirubin value > 3x the upper limit of normal (ULN)
  - Baseline prothrombin time or partial thromboplastin time > 1.5x ULN

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
SCD	Minimum recommended dose: 3×10^6 CD34+ cells/kg of body weight IV	Not applicable

VI. Product Availability

Single-dose cell suspension: one to four infusion bags which contain 1.7 to 20×10^6 cells/mL suspended in cryopreservation solution

VII. References

1. Lyfgenia Prescribing Information. Somerville, MA: Bluebird Bio, Inc.; December 2023. Available at: https://www.bluebirdbio.com. Accessed November 18, 2024.
2. ClinicalTrials.gov. A Study Evaluating the Safety and Efficacy of bb1111 in Severe Sickle Cell Disease. Last updated August 23, 2023. Available at: https://clinicaltrials.gov/ct2/show/NCT02140554. Accessed November 18, 2024.
3. Kanter J, Liem RI, Bernaudin F, et al. American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation. *Blood Adv*. 2021;5(18):3668-3689. doi:10.1182/bloodadvances.2021004394C
4. 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
5. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Evidence-based management of sickle cell disease: Expert Panel Report, 2014. National Heart, Lung, and Blood Institute (NHLBI). Available at: https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. Accessed November 18, 2024.
6. Clinical Pharmacology [database online]. Philadelphia, PA: Elsevier. Updated periodically. Available at: http://www.clinicalkey.com/pharmacology. Accessed November 18, 2024.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J3394	Injection, lovotibeglogene autotemcel, per treatment

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	03.10.23	05.23
Drug is now FDA-approved – criteria updated per FDA labeling: clarified that only β^s/β^s genotype genetic confirmation is required per population studied in clinical trial; added criterion for documentation of ≥ 4 severe VOEs within the past 24 months along with the pivotal trial definition of a severe VOE; revised hydroxyurea failure criterion for hydroxyurea to be tried for ≥ 6 months and removed requirement for ≥ 1 VOE while taking hydroxyurea; revised alpha thalassemia criterion to member does not have "≥ 2" α-globin gene deletions; added criteria that member is negative for the presence of active HIV, hepatitis B virus, hepatitis C virus, advanced liver disease, current malignancy and current immunodeficiency disorder; clarified minimum Lyfgenia dose required; approval duration revised to 6 months to allow for gene therapy preparation and clarified infusion is "one-time"; references reviewed and updated.	01.16.24	02.24
Added HCPCS code [J3394] and removed HCPCS codes [J3590, C9399].	06.03.24	
1Q 2025 annual review: added criterion for documentation of member's body weight for verification of weight-based dose; references reviewed and updated.	11.18.24	02.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and

limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.