Neighborhood Health Plan OF RHODE ISLAND™
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Lyfgenia® (lovotibeglogene autotemcel)
(Intravenous)

Effective Date: 05/01/2024
Review Date: 03/20/2024, 07/17/2024, 10/09/2024

Scope: Medicaid, Commercial, Medicare-Medicaid Plan (MMP)

I. Length of Authorization

Coverage will be provided for one treatment course (1 dose of Lyfgenia) and may not be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- A single dose of Lyfgenia containing a minimum of 3.0×10^6 CD34+ cells/kg of body weight, in one or more infusion bags

B. Max Units (per dose and over time) [HCPS Unit]:

- A single dose of Lyfgenia containing a minimum of 3.0×10^6 CD34+ cells/kg of body weight, in one or more infusion bags

III. Summary of Evidence

Lyfgenia (lovotibeglogene autotemcel) is indicated for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events (VOEs). Lyfgenia's approval is based upon efficacy demonstrated in a single-arm, 24-month, open-label, multicenter Phase 1/2 study that continued into a long-term follow-up study. Of the 43 patients enrolled with a history of at least 4 VOEs in the previous 24 months, 36 patients successfully received myeloablative busulfan conditioning and Lyfgenia. The efficacy outcomes were complete resolution of VOEs (VOECR) and severe VOEs (sVOE-CR) between 6 months and 18 months after infusion of Lyfgenia. 28/32 patients had complete resolution of VOEs (88%, 95% CI: 71,97) and 30/32 had complete resolution of severe VOEs (94%, 95% CI: 79,99). The most common adverse reactions ≥ Grade 3 (incidence ≥ 20%) were stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia.

IV. Initial Approval Criteria [1]

> Submission of medical records (chart notes) related to the medical necessity criteria is REQUIRED on all requests for authorizations. Records will be reviewed at the time of submission. Please provide documentation related to diagnosis, step therapy, and clinical markers (i.e. genetic and mutational testing) supporting initiation when applicable. Please provide documentation via direct upload through the PA web portal or by fax.

Coverage is provided in the following conditions:

- Patient is at least 12-50 years of age; **AND**

- Provider has considered use of prophylaxis therapy for seizures prior to initiating myeloablative conditioning; **AND**
- Patient will be monitored for hematologic malignancies periodically after treatment; **AND**
- Must not be administered concurrently with live vaccines while immunosuppressed; **AND**
- Patient does not have a history of hypersensitivity to dimethyl sulfoxide (DMSO) or dextran 40; **AND**
- Patient is HIV negative as confirmed by a negative HIV test prior to mobilization (*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.)*; **AND**
- 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, vexelotor, crizanlizumab) for at least 2 months prior to mobilization; **AND**
    - Prophylactic HIV anti-retroviral therapy *(Note: Patients receiving prophylactic ART should stop 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., Casgevy™ (exagamglogene autotemcel)] *****; **AND**
- Patient is a candidate for autologous hematopoietic stem cell transplant (HSCT) [i.e., patient does not have deficiencies in bone marrow, lung, heart, or liver function]; **AND**
- Patient does not have a known 10/10 human leukocyte antigen matched related donor willing to participate in an allogeneic HSCT; **AND**
- Patient does not have a history of previous hematopoietic stem cell transplant (HCST); **AND**
- 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 does not have a potential contraindication to any product or procedure required for successful gene therapy treatment including (but not limited to):
    - Plerixafor; **AND**
    - Busulfan; **AND**
    - Red blood cell infusion; **AND**
- Patient will undergo treatment at a manufacturer approved Qualified Treatment Center (QTC); **AND**
- Lyfgenia is prescribed by, or in consultation with, a specialist in hematology; **AND**

Sickle Cell Disease [1-3] † Φ

- Patient has a confirmed diagnosis of sickle-cell disease (includes genotypes βS/βS or βS/β0 or βS/β+) 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 and formulary add-on therapy (e.g., Adakveo (crizanlizumab), etc.); **AND**
- Patient has a contraindication to or is not indicated for treatment with Casgevy™ (exagamglogene autotemcel); **AND**
- Patient experienced four or more vaso-occlusive events/crises (VOE/VOC)***** in the previous two years while adhering to the above therapy

**VOE/VOC is defined as an event requiring a visit to a medical facility for evaluation which results in a diagnosis of such being documented due to one (or more) of the following: acute pain, acute chest syndrome, acute splenic sequestration, acute hepatic sequestration, priapism lasting > 2 hours AND necessitating subsequent interventions such as opioid pain management, non-steroidal anti-inflammatory drugs, RBC transfusion, etc.*

*****Requests for subsequent use of lovotibeglogene after receipt of exagamglogene autotemcel will be evaluated on a case-by-case basis

MMP members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements.

† FDA Approved Indication(s); **‡** Compendia Recommended Indication(s); **Φ** Orphan Drug

V. Renewal Criteria [1,3]

- Coverage cannot be renewed.

VI. Dosage/Administration [1]

Indication	Dose
Sickle-Cell Disease	Lyfgenia is provided as a single dose for infusion containing a suspension of CD34+ cells in one to four infusion bags. • The minimum recommended dose of Lyfgenia is 3×10^6 CD34+ cells/kg.
- *Mobilization should occur using a CXCR4 (e.g., plerixafor) in the absence of G-CSF* - *Myeloablative conditioning (e.g., busulfan) should not occur until Lyfgenia (and back-up cell collection) are received. Prophylaxis for hepatic veno-occlusive disease (VOD)/hepatic sinusoidal obstruction syndrome should be considered.* - *Lyfgenia must be administered at least 48 hours after the last dose of the myeloablative conditioning.* - *Lyfgenia is for autologous use only. Before infusion, confirm that the patient's identity matches the unique patient identifiers on the Lyfgenia bag(s). Do not infuse if the information on the patient-specific label does not match the intended patient.*	

VII. Billing Code/Availability Information

HCPCS:

- J3394 – injection, lovotibeglogene autotemcel, per treatment

NDC:

- Lyfgenia is supplied in one to four infusion bags containing a frozen suspension of genetically modified autologous cells, enriched for CD34+ cells, 20 mL infusion bag, overwrap, and metal cassette: 73554- 1111-xx

VIII. References

1. Lyfgenia [package insert]. Somerville, MA; Bluebird Bio, Inc., December 2023. Accessed December 2023.
2. Kanter J, Thompson AA, Pierciey FJ Jr, et al. Lovo-cel gene therapy for sickle cell disease: Treatment process evolution and outcomes in the initial groups of the HGB-206 study. Am J Hematol. 2023 Jan;98(1):11-22. doi: 10.1002/ajh.26741. Epub 2022 Oct 10. PMID: 36161320; PMCID: PMC10092845.
3. Bender MA, Carlberg K. Sickle Cell Disease. 2003 Sep 15 [Updated 2022 Nov 17]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1377/.
4. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014 Sep 10;312(10):1033-48.
5. Tisdale JF, Pierciey FJ, Bonner M, et al. (2020) Safety and feasibility of hematopoietic progenitor stem cell collection by mobilization with plerixafor followed by apheresis vs bone marrow harvest in patients with sickle cell disease in the multi-center HGB-206 trial. Am J Hematol E239–E242. https://doi.org/10.1002/ajh.25867.
6. Palmer J, McCune JS, Perales M-A, et al. (2016) Personalizing Busulfan-Based Conditioning: Considerations from the American Society for Blood and Marrow Transplantation Practice Guidelines Committee. Biol Blood Marrow Transplant 1915–1925. https://doi.org/10.1016/j.bbmt.2016.07.013
7. Brunson A, Keegan THM, Bang H, et al. (2017) Increased risk of leukemia among sickle cell disease patients in California. Blood 130:1597–1599. doi: 10.1182/blood-2017-05-783233.
8. Seminog OO, Ogunlaja OI, Yeates D, Goldacre MJ (2016) Risk of individual malignant neoplasms in patients with sickle cell disease: English national record linkage study. J R Soc Med 109:303–309. doi: 10.1177/0141076816651037.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
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
D57.03	Hb-SS disease with cerebral vascular involvement
D57.04	Hb-SS disease with crisis with other specified complication
D57.1	Sickle-cell disease without crisis
D57.20	Sickle-cell/Hb-C disease without crisis
D57.211	Sickle-cell/Hb-C disease with acute chest syndrome
D57.212	Sickle-cell/Hb-C disease with splenic sequestration
D57.213	Sickle-cell/Hb-C disease with cerebral vascular involvement
D57.214	Sickle-cell/Hb-C disease with crisis with other specified complication

D57.219	Sickle-cell/Hb-C disease with crisis unspecified
D57.3	Sickle-cell trait
D57.40	Sickle-cell thalassemia without crisis
D57.411	Sickle-cell thalassemia with acute chest syndrome
D57.412	Sickle-cell thalassemia with splenic sequestration
D57.413	Sickle-cell thalassemia, unspecified, with cerebral vascular involvement
D57.414	Sickle-cell thalassemia, unspecified, with crisis with other specified complication
D57.419	Sickle-cell thalassemia with crisis unspecified
D57.42	Sickle-cell thalassemia beta zero without crisis
D57.431	Sickle-cell thalassemia beta zero with acute chest syndrome
D57.432	Sickle-cell thalassemia beta zero with splenic sequestration
D57.433	Sickle-cell thalassemia beta zero with cerebral vascular involvement
D57.434	Sickle-cell thalassemia beta zero with crisis with other specified complication
D57.439	Sickle-cell thalassemia beta zero with crisis unspecified
D57.44	Sickle-cell thalassemia beta plus without crisis
D57.451	Sickle-cell thalassemia beta plus with acute chest syndrome
D57.452	Sickle-cell thalassemia beta plus with splenic sequestration
D57.453	Sickle-cell thalassemia beta plus with cerebral vascular involvement
D57.454	Sickle-cell thalassemia beta plus with crisis with other specified complication
D57.459	Sickle-cell thalassemia beta plus with crisis unspecified
D57.80	Other sickle-cell disorders without crisis
D57.811	Other sickle-cell disorders with acute chest syndrome
D57.812	Other sickle-cell disorders with splenic sequestration
D57.813	Other sickle-cell disorders with cerebral vascular involvement
D57.814	Other sickle-cell disorders with crisis with other specified complication
D57.819	Other sickle-cell disorders with crisis, unspecified

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCA/LCD): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Policy Rationale:

Lyfgenia was reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use Lyfgenia according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For INTEGRITY (MedicareMedicaid Plan) members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan