Lyfgenia® (lovotibeglogene autotemcel)
(Intravenous)

Document Number: IC-0743

Last Review Date: 01/06/2026
Date of Origin: 01/04/2024
Dates Reviewed: 01/2024, 01/2025, 02/2025, 07/2025, 01/2026

I. Length of Authorization

- Initial: Prior authorization validity will be provided initially for one treatment course (1 dose of Lyfgenia).
- Renewal: Prior authorization validity may not be renewed.

II. Dosing Limits

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

- 1 billable unit for one dose

III. Initial Approval Criteria [1]

Submission of supporting clinical documentation (including but not limited to medical records, chart notes, lab results, and confirmatory diagnostics) related to the medical necessity criteria is REQUIRED on all requests for authorizations. Records will be reviewed at the time of submission as part of the evaluation of this request. 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**.** Failure to submit the medical records may result in the denial of the request due to inability to establish medical necessity in accordance with policy guidelines.

Prior authorization validity is provided in the following conditions:

- Patient is at least 12 years of age; **AND**
- Provider has considered use of prophylaxis therapy for seizures with agents other than phenytoin prior to initiating myeloablative conditioning; **AND**
- Patient will be monitored for hematologic malignancies periodically after treatment; **AND**
- Provider will confirm that patient will not receive live vaccines concurrently while 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 (*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*

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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**
    - Iron chelators for at least 7-days prior to mobilization or conditioning and for 6 months post-treatment for myelosuppressive iron chelators (e.g., deferiprone) OR 3-months post-treatment for non-myelosuppressive iron chelators; **AND**
    - Disease-modifying agents (e.g., L-glutamine, 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 used for the treatment of sickle cell disease [e.g., Casgevy® (exagamglogene autotemcel)] **§**; **AND**
- Patient is a candidate for autologous hematopoietic stem cell transplant (HSCT) and has not had a prior allogeneic transplant; **AND**
- For patients under 18 years of age, the patient does not have a known and available suitable 10/10 human leukocyte antigen matched related donor willing to participate in an allogeneic HSCT; **AND**
- Patient will be transfused at least twice (once each month) prior to mobilization to reach a target hemoglobin (Hb) of 8-10 g/dL (less than 12 g/dL) and < 30% hemoglobin S (HbS); **AND**

§ *Requests for subsequent use of lovotibeglogene autotemcel after receipt of other gene therapies used for the treatment of sickle cell disease (e.g., exagamglogene autotemcel) will be evaluated on a case-by-case basis*

Sickle Cell Disease [1-3] † Φ

- 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**

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- Patient has uncontrolled disease despite treatment with hydroxyurea OR crizanlizumab at any point in the past *(Note: trial of crizanlizumab not applicable to patients less than 16 years of age)* OR has experienced intolerance OR has required repeat transfusions to treat symptomatic disease and/or reduce the risk of stroke; **AND**
- Patient has severe, symptomatic disease despite treatment with supportive care measures, as experienced by one or more of the following:
    - Patient has echocardiographic evidence of a tricuspid regurgitant jet velocity (TRJV) of > 2.5 m/s; **OR**
    - Patient has had or has a history of an overt stroke (Note: Defined as a sudden neurologic change lasting more than 24 hours that is accompanied by cerebral MRI changes); **OR**
    - Patient has experienced an 'acute chest syndrome' episode, defined as an acute event with pneumonia-like symptoms and the presence of a new pulmonary infiltrate in the previous 2 years; **OR**
    - Patient experienced two or more vaso-occlusive events/crises (VOE/VOC) ***** in the previous year

**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.*

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

IV. Renewal Criteria [1]

- Duration of authorization has not been exceeded *(refer to Section I)*.

V. 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 plerixafor *- 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.*	

VI. Billing Code/Availability Information

HCPCS:

- J3394 – Injection, lovotibeglogene autotemcel, per treatment; 1 billable unit = 1 treatment

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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

VII. References

1. Lyfgenia [package insert]. Somerville, MA; Bluebird Bio, Inc., December 2023. Accessed November 2025.
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 2025 Feb 13]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. 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.
9. 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

Appendix A – Non-Quantitative Treatment Limitations (NQTL) Factor Checklist

Non-quantitative treatment limitations (NQTLs) refer to the methods, guidelines, standards of evidence, or other conditions that can restrict how long or to what extent benefits are provided under a health plan. These may include things like utilization review or prior authorization. The utilization management NQTL applies comparably, and not more stringently, to mental health/substance use disorder (MH/SUD) Medical Benefit Prescription Drugs and medical/surgical (M/S) Medical Benefit Prescription Drugs. The table below lists the factors that were considered in designing and applying prior

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authorization to this drug/drug group, and a summary of the conclusions that Prime's assessment led to for each.

Factor	Conclusion
Indication	Yes: Consider for PA
Safety and efficacy	Yes: Consider for PA
Potential for misuse/abuse	No: PA not a priority
Cost of drug	Yes: Consider for PA

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 dactylitis
D57.09	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 dactylitis
D57.218	Sickle-cell/Hb-C disease with crisis with other specified complication
D57.219	Sickle-cell/Hb-C disease with crisis, unspecified
D57.40	Sickle-cell thalassemia without crisis
D57.411	Sickle-cell thalassemia, unspecified, with acute chest syndrome
D57.412	Sickle-cell thalassemia, unspecified, with splenic sequestration
D57.413	Sickle-cell thalassemia, unspecified, with cerebral vascular involvement
D57.414	Sickle-cell thalassemia, unspecified, with dactylitis
D57.418	Sickle-cell thalassemia, unspecified, with crisis with other specified complication
D57.419	Sickle-cell thalassemia, unspecified, with crisis
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 dactylitis

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D57.438	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 dactylitis
D57.458	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 dactylitis
D57.818	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		
Jurisdictio	**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.

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Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdictio	**Applicable State/US Territory**	**Contractor**
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
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

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