Molina Clinical Policy
Lyfgenia (lovotibeglogene autotemcel): Policy No. 448

Last Approval: 12/11/2024
Next Review Due By: December 2025

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

This policy addresses the use of Lyfgenia for the treatment of individuals with sickle cell disease.

Sickle cell disease (SCD) is an inherited (autosomal recessive) hemoglobinopathy characterized by chronic hemolytic anemia and intermittent, painful, vaso-occlusive crisis (VOC). A VOC is defined as pain resulting from tissue ischemia caused by vaso-occlusion most commonly in the bone(s) and bone marrow. Those with greater than 3 hospitalizations for VOC per year are at increased risk for early death. Almost all people with sickle cell disease experience one or more vaso-occlusive crises in their lives.

The disease can occur in individuals of any ethnicity, but is most common in those of African, Caribbean, Mediterranean, Middle Eastern, and Indian ancestry. Approximately 1 in 500 African American infants born in the United States are diagnosed with SCD which has led to screening panels in newborns. There are about 100,000 individuals with SCD in the United States. About 20,000 are considered to have severe sickle cell disease. Specific pathogenic mutations in the beta globin gene cause sickle cell anemia. Sixty to seventy percent of SCD diagnosed in the United States are caused by the same homozygous pathogenic variant known as hemoglobin S (HbS).The trademark laboratory feature of SCD is the presence of sickle-shaped red blood cells on peripheral blood smear. Red blood cells sickle at low oxygen tension which obstructs vessels, incites inflammation, and causes endothelial dysfunction. SCD is the leading cause of ischemic stroke in children. Chronic complications from sickle cell anemia shorten life span by 20 years, on average. Individuals with sickle cell disease also endure stigma and bias in attempting to get care and face additional mental health challenges as they cope with this disorder (JAMA 2020; Kavanaugh 2022).

Current therapies for sickle cell anemia include Hydroxyurea, L-glutamine (Endari), crizanlizumab (Adakveo), voxelotor (oxbryta) and allogeneic Hematopoietic Stem-cell transplantation (HSCT). Apart from HSCT, all therapies are only partially effective, and none prevent VOCs. In allogeneic HSCT, donors need to be well matched at three or more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1) (Rodgers et al. 2024). Those without a well-matched donor would not be able to access allogeneic stem cell transplant therapy. Less than 20% of eligible patients have a well-matched donor. HSCT is the only proven curative therapy to date. Gene-cell therapy, which involves the autologous transplantation of genetically modified hematopoietic stem cells, is a new therapeutic option that is potentially curative.

Lovotibeglogene autotemcel (bb1111, BB305, Lovo-cel, 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 and a history of vaso-occlusive event. Lyfgenia utilizes a lentiviral vector (LVV) to introduce a modified *β*-globin$^{A\text{-}T87Q}$ gene into hematopoietic stem cells. The result is a sustainable and potentially curative alternative to chronic transfusions and other standard of care therapies such as hydroxyurea. Once the $\beta^{A\text{-}T87Q}$-globin gene is incorporated into hematopoietic stem cells, adult hemoglobin is produced at levels that may eliminate or significantly reduce vaso-occlusive events. The globin protein produced from Lyfgenia, HbA^{T87Q}, not only increases the amount of functional adult hemoglobin, it also affords some degree of anti-sickling properties and allows for tracking expression levels.

Administration of lovo-cel involves harvesting the patient's stem cells followed by selecting for CD34+ markers then transduction with lentiglobin. Once enough transduced cells are grown, the cells are shipped back to the treatment center in preparation for transfusion into the patient. The patient will then go through standard myeloablation procedures and remain in the hospital after receiving their genetically engineered cells while engraftment occurs.

FDA approval of Lyfgenia is based on data from a phase 1 / 2 trial evaluating its potential efficacy and safety. There is a **black box** warning on the FDA label for Lyfgenia that states, patients treated with LYFGENIA may develop hematologic malignancies and should have lifelong monitoring. Monitoring for hematologic malignancies with a complete blood count (with differential) at least every 6 months for at least 15 years after treatment with LYFGENIA, and integration site analysis at Months 6 and 12 is recommended. Additional data requested by the FDA later in June of 2023 is reported under subsection, "Summary of Medical Evidence" below.

RELATED POLICIES

MCP-447: Casgevy (exagamglogene autotemcel) for Sickle Cell Disease

COVERAGE POLICY

All Gene Therapy requests require Molina Medical Director review.

Lyfgenia (lovo-cel or lovotibeglogene autotemcel) for the treatment of SCD may be **considered medically necessary** when **ALL** the following clinical criteria with documentation are met:

1. A diagnosis of severe sickle cell disease defined by:
    a. Genetic testing confirming severe sickle cell disease genotype (βS/βS, βS/β0, or βS/β+); AND
    b. History of at least four severe vaso-occlusive events (VOE) within the previous two years while receiving appropriate supportive care. A severe VOE is defined as an episode of acute pain "with no medically determined cause other than a vaso-occlusion, requiring a ≥ 24-hour hospital or Emergency Room (ER) observation unit visit or at least 2 visits to a day unit or ER over 72 hours with both visits requiring intravenous treatment. Other VOE's that would count as severe:
        i. Acute pain event requiring a visit to a medical facility & administration of pain medications (opioids or IV nonsteroidal anti-inflammatory drugs or RBC transfusions)
        ii. Acute chest syndrome indicated by a new pulmonary infiltrate associated with pneumonia - like symptoms, pain or fever
        iii. Priapism lasting > 2 hours & requiring a visit to a medical facility.
        iv. Splenic sequestration, defined by an enlarged spleen, left upper quadrant pain and an acute decrease in hemoglobin concentration ≥ 2g/dL.
        v. Acute hepatic sequestration
2. Absence of genetic mutations leading to inactivation of 2 or more α-globin genes
3. Member is 12 years of age or greater but less than or equal to 50 years of age
4. Have either experienced hydroxyurea (HU) failure at any point in the past or must have intolerance to HU per treating physician
5. Karnofsky performance status of ≥ 60 (≥16 years of age) or a Lansky performance status of ≥60 (<16 years of age)
6. Eligible to undergo stem cell transplant procedures including mobilization with plerixafor, and myeloablative conditioning with busulfan (No contraindications to either)

7. Baseline oxygen saturation ≥ 90% without supplemental oxygen (excluding periods of SCD crisis or infection)

8. Baseline carbon monoxide diffusing capacity (DLCO) ≥ 50% (corrected for Hb) in the absence of infection

9. Baseline left ventricular ejection fraction (LVEF) ≥ 45%

10. No significant pulmonary hypertension at baseline. Significant pulmonary hypertension is defined by the requirement for ongoing pharmacologic treatment or the consistent or intermittent use of supplemental home oxygen

11. Baseline estimated glomerular filtration rate (eGFR) ≥ 70 mL/min/1.73 m2, as determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

12. The member is not positive for human immunodeficiency virus type 1 or 2 (HIV-1 and HIV-2), hepatitis B virus, or Hepatitis C virus, human T-lymphotrophic virus-1 (HTLV-1) or HTLV-2, syphilis (RPR). Testing for toxoplasmosis, Trypanosoma cruzi, or West Nile Virus, malaria, tuberculosis should be completed if clinically or regionally indicated and be negative

13. The member does not have clinically significant, active bacterial, fungal, viral or parasitic infections

14. The member has adequate bone marrow function as defined by an absolute neutrophil count of > 1000/µL (> 500/µL for subjects on HU treatment) and a platelet count > 100,000/µL

15. Member does not have advanced liver disease as indicated by alanine aminotransferase or direct bilirubin < 3 times the upper limit of normal and baseline prothrombin time or partial thromboplastin time < 1.5 x the upper limit of normal

16. For subjects who have been receiving chronic transfusion therapy for > 1 year and have evidence of iron overload (serum ferritin levels >1000 ng/mL) or for those that may have advanced liver disease, a liver MRI is required. Liver MRI should not show evidence of advanced liver disease (cirrhosis). If MRI is suggestive or equivocal of active hepatitis, significant fibrosis, cirrhosis or liver iron concentration ≥ 15mg/g and member is ≥ 18 years of age, a liver biopsy is required. Liver biopsy should not show evidence of active hepatitis, cirrhosis, or bridging fibrosis. For those under 18 years of age, equivocal or suggestive MRI findings would be exclusionary. A biopsy can be submitted if the treating physician believes this will help clarify MRI findings and allow eligibility

17. For subjects who have been receiving chronic transfusion therapy for > 1 year and have evidence of iron overload (serum ferritin levels >1000 ng/mL), a cardiac MRI is required. Cardiac MRI should not show Cardiac T2* <10 ms

18. Does not have an HLA matched related donor available

19. Has not had previous allogeneic transplant

20. Member has not received a gene therapy, or is not being considered for other gene therapies, or investigational cellular therapy for sickle cell disease

21. Females of childbearing potential and males capable of fathering a child have been counseled on the use of effective contraception during treatment (from start of mobilization through at least 6 months after administration of lovo-cel) AND advised of the risks associated with conditioning agents

22. For females of childbearing potential: Member is not pregnant or breast-feeding: Negative serum pregnancy test within the past 30 days
    NOTE: A negative serum pregnancy test must be confirmed prior to the start of mobilization and re-confirmed prior to conditioning procedures and before lovo-cel administration

23. No family history or immediate family member with a known or suspected Familial Cancer Syndrome

24. No prior or current malignancy, or immunodeficiency disorder, except previously treated, non-life threatening, cured tumors such as squamous cell carcinoma of the skin

25. No chromosomal abnormality / mutation leading to an increased risk for myelodysplastic syndrome or acute myeloid leukemia

26. No History of significant bleeding disorder

27. Diagnosis of significant psychiatric disorder that could impede the ability to participate in the processes required to generate and deliver the Lyfgenia medication

CONTINUATION OF THERAPY
Repeat administration is experimental and investigational since the safety and efficacy beyond one treatment has not been studied and is not indicated in the current FDA approval for lovo-cel. The evidence is insufficient to determine the effects on net health outcomes.

LIMITATIONS AND EXCLUSIONS
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.

There are no contraindications listed in the manufacturer's labeling at this time.

The following are considered **experimental, investigational, and unproven** based on insufficient evidence:
1. Any indications other than those listed above (e.g., sickle cell disease)
2. Prior treatment with any form of HSCT, lovo-cel, or other gene therapy

DURATION OF APPROVAL: Duration sufficient for **ONE** single course of treatment

PRESCRIBER REQUIREMENTS: Prescribed by, or in consultation with, a board-certified hematologist

AGE RESTRICTIONS: ≥ 12 years and ≤ 50 years at the time of infusion
The age across the trials was 12 to 50 years of age.

DOSING CONSIDERATIONS: Cell suspension for IV infusion. For autologous use only.
- Patients are required to undergo HSC mobilization followed by apheresis to obtain CD34+ cells for lovo-cel manufacturing.
- Dosing is based on the number of CD34+ cells in the infusion bag(s) per kg of body weight. Minimum recommended dose: 3 x10^6 CD34+ cells/kg as a one-time IV infusion
- Myeloablative conditioning must be administered before infusion of lovo-cel.

ADMINISTRATION:
1. Lovo-cel is considered a provider-administered therapy in a Qualified Treatment Center by a physician(s) with experience in HSCT and in the treatment of patients with SCD.
2. Prior to beginning the mobilization, anti-retrovirals, Hydroxyurea and iron chelation should be discontinued – see package insert for details.
3. Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or rendering a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Phase 1 / 2 Study

Accelerated approval for lovo-cel is based on results from interim analysis of one Phase 1/2 clinical trial (HGB-206). HGB-206 (NCT02140554) trial is a non-randomized, multicenter, open-label, single arm study of 50 patients with severe SCD. The protocol was optimized during the trial and with each optimization resulting in a different treatment group. There were a total of 3 groups (A, B, & C). Each group differed in the treatment process, cell collection or manufacturing process. Study 1-C of HGB-206 was the main source of data for FDA approval. Group C was treated with the newest protocol and manufactured BB305 lentiviral vector encoding the modified B-globin gene. Group C was composed of 32 patients, ages 12-50 years of age with severe SCD indicated by both genotype and phenotype. Genotypes βS/βS, βS/β0, or βS/β+ were considered severe. Phenotypically, severe SCD is defined as having a clinical history of ≥ 4 VOEs over the previous 2 years. 32 patients had been followed long enough at the latest data cut to be included in the analysis. Importantly, patients with a history of stroke were included in group C.

The primary efficacy endpoint was the proportion of subjects without VOEs and severe VOEs post 6-18 months Lyfgenia infusion.

Results from Study 1-C of HGB-206

Clinical Attribute	Results
VOE-CR n/N(%) [95% CI]	 28/32 [71, 97]
sVOE-CR n/N(%) [95% CI]	 30/32 (94%) [79, 99]

(s)VOE-CR = elimination of (s)VOEs between 6 and 18 months post infusion with LYFGENIA.

Five patients with history of stroke or vasculopathy were treated in Study 1-C. 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.

Three patients died during LYFGENIA clinical trials; one from sudden cardiac death due to underlying disease and two from acute myeloid leukemia who were treated with an earlier version of LYFGENIA using a different manufacturing process and transplant procedure (Study 1, Group A). One patient with an alpha thalassemia trait from the group C trial group developed myelodysplastic syndrome trait (FDA 2023).

Approximately 49% of patients were prescribed opioids after the primary evaluation period up to 24 months, for sickle cell and non-sickle cell-related pain. A secondary endpoint, change in hemoglobin from baseline, improved from 8.5 g/dl at baseline to a median of 11 g/dl at 6 months and was sustained throughout 36 months. All Hemolysis markers improved and approximated normal levels (Kanter et al. 2022). Final data for study HGB-206 is not yet published.

The 13 year long term extension study, LTF-307 (NCT04628585) is an on-going, global, multi-site, rollover study designed to evaluate the safety and efficacy of lovo-cel in subjects who previously received lovo-cel in study HB206 for the treatment of sickle cell disease. Study HGB-210 (NCT04293185) has started and is aimed at pediatric patients aged 2-11 years of age with SCD. Completion for this study is estimated to be in April of 2027.

National and Specialty Organizations

Institute for Clinical and Economic Review (ICER) published a final evidence report supporting the value of lovo-

cel for the treatment of Sickle cell disease (July 2023). The report focused on the clinical benefits of lovo-cel but noted cost-effectiveness comparisons to standard clinical management for severe Sickle cell disease, could not be completed without the actual prices of therapies. The systematic review suggests lovo-cel is likely to "substantially" improve quality and length of life for patients with severe SCD. The magnitude of this superiority is still uncertain due to known risks with myeloablative conditioning and unknown durability.

National Heart, Lung and Blood Institute management guidelines notes, "The clinical benefit of HSCT or gene therapy vs regular blood transfusion therapy for secondary prevention of cerebral infarcts in children and adults with preexisting silent cerebral infarct should be determined."

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

Code	Description
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96415	Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure)

HCPCS (Healthcare Common Procedure Coding System)

Code	Description
J3394	Injection, lovotibeglogene autotemcel, per treatment

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

12/11/2024	Added requirement of Molina Medical Director review. Summary of Evidence and References updated.
02/14/2024	Thresholds for baseline health markers necessary to receive Lyfgenia were updated after unpublished data was made available by the manufacturer. These included an increase to baseline cardiac ejection fraction to 45% from 40%, and DLCO to 45% from 40%, baseline O2 sat to 90% from 85% and specifications about when a liver biopsy may be needed to assess liver health and iron deposition.
12/13/2023	New policy. IRO Review completed December 2023 by a practicing physician board-certified in Pediatric Hematology/Oncology.

REFERENCES

1. Clinicaltrials.gov. NCT02140554. A Phase 1/2 Study Evaluating Gene Therapy by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo With the LentiGlobin BB305 Lentiviral Vector in Subjects With Severe Sickle Cell Disease. Last updated October 8, 2024. Accessed November 26, 2024
2. Clinicaltrials.gov. NCT04293185. A study evaluating gene therapy with BB305 Lentiviral Vector in Sickle cell disease. Accessed Last updated July 9, 2024. Accessed November 26, 2024.
3. Clinicaltrials.gov. NCT04628585. Long-term follow-up of subjects with Sickle Cell disease with ex-vivo gene therapy. Last updated May 24, 2023. Last updated June 26, 2024. Accessed November 25, 2024.
4. DeBaun MR, Jordan LC, King AA, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Adv. 2020 Apr 28;4(8):1554-1588. doi: 10.1182/bloodadvances.2019001142. PMID: 32298430; PMCID: PMC7189278.
5. Eastern Cooperative Oncology Group (ECOG) Performance Status. https://ecog-acrin.org/resources/ecog-performance-status. Accessed November 25, 2024.
6. Field JJ, Vichinsky EP. Overview of the management and prognosis of sickle cell disease. Updated July 18, 2024. Accessed November 25, 2024. http://www.uptodate.com/.
7. Hayes. Health technology assessment: Lovotibeglogene Autotemcel (Lyfgenia; Bluebird Bio) for Sickle Cell Disease. Published December 11, 2023. Updated October 2, 2024. Accessed November 25, 2024. https://evidence.hayesinc.com
8. Kanter J, Walters MC, Krishnamurti L, et al. Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease. N Engl J Med. 2022 Feb

17;386(7):617-628. doi: 10.1056/NEJMoa2117175. Epub 2021 Dec 12. PMID: 34898139.
9. Kanter J, Thompson AA, Piercley 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.
10. Kavanagh PL, Fasipe TA, Wun T. Sickle Cell Disease: A Review. JAMA. 2022 Jul 5;328(1):57-68. doi: 10.1001/jama.2022.10233. PMID: 35788790.
11. LOVO-US_SR-0027 - Inclusion and Exclusion criteria for HGB-206 Group C (Unpublished protocol changes form manufacturer). Information provided by Bluebird Bio, Inc. Received February 2024.
12. LYFGENIA® (lovotibeglogene autotemcel) FDA Prescribing information. Published December 2023. https://www.fda.gov/media/174610/download?attachment
13. National Heart, Lung and Blood Institute (NHLBI). Evidence-based management of sickle cell disease: Expert panel report, 2014. Accessed November 25, 2024. https://www.nhlbi.nih.gov/health-topics/evidence-based-management-sickle-cell-disease.
14. Rodgers GP, George A, Strouse J. Hydroxyurea use in sickle cell disease. http://www.uptodate.com/. Updated October 21, 2024. Accessed November 25, 2024.
15. Sickle Cell Disease Association of America (SCDAA). What is sickle cell disease (SCD)? https://www.sicklecelldisease.org/sickle-cell-health-and-disease/types/. Accessed November 25, 2024.
16. 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. doi: 10.1001/jama.2014.10517. Erratum in: JAMA. 2014 Nov 12;312(18):1932. Erratum in: JAMA. 2015 Feb 17;313(7):729. PMID: 25203083.