Pharmacy Management Drug Policy

SUBJECT: Lyfgenia-lovotibeglogene autotemcel
POLICY NUMBER: PHARMACY-119
EFFECTIVE DATE: 06/2024
LAST REVIEW DATE: 07/17/2026

If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. This drug policy applies to the following line/s of business:

Policy Application

Category:	☒ Commercial Group (e.g., EPO, HMO, POS, PPO)	☒ Medicare Advantage
	☒ On Exchange Qualified Health Plans (QHP)	☐ Medicare Part D
	☒ Off Exchange Direct Pay	☒ Essential Plan (EP)
	☒ Medicaid & Health and Recovery Plans (MMC/HARP)	☒ Child Health Plus (CHP)
	☐ Federal Employee Program (FEP)	☐ Ancillary Services
	☒ Dual Eligible Special Needs Plan (D-SNP)	

DESCRIPTION:

Sickle Cell Disease (SCD) represents a group of genetic disorders characterized by structural abnormalities in hemoglobin (Hb). A single amino acid substitution is responsible for the production of sickle hemoglobin (HbS). There are several variant genotypes of the normal adult hemoglobin (HbAA) that cause SCD, with the most prevalent including HbSS, HbSC, HbS/β+ thalassemia, and HbS/β0 thalassemia.[1] SCD affects millions worldwide, including an estimated 100,000 Americans.[2]

The main driver of sickle cell pathogenesis is polymerization of deoxygenated HbS, creating a distorted sickle shaped red blood cell (RBC). These rigid and inflexible RBCs have a higher propensity for hemolysis and adhering to vascular endothelial cells causing vaso-occlusion.[3] The repeated sickling and hemolysis causes a variety of complications including vaso-occlusive crisis (VOCs), hemolytic anemia, acute chest syndrome, stroke, pulmonary hypertension, deep vein thrombosis, infection, and splenic sequestration. VOCs are one of the main reasons for healthcare encounters.[4]

The main goal of SCD treatment is preventing and managing disease complications such as acute and chronic pain, and cerebrovascular, cardiopulmonary, and kidney disease. Lifestyle modifications, health screenings and other prevention strategies are recommended to optimize care. Disease modifying therapies (e.g., hydroxyurea, L-glutamine, voxelotor, and crizanlizumab) target various pathways involved in SCD to prevent sickling, reduce comorbid complications, and decrease VOCs. Allogenic hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy but carries many risks (e.g., graft failure, infections, graft-versus-host disease, death) and <20% of individuals have a suitable matched donor.[1,5]

Lyfgenia (lovotibeglogene autotemcel)

On December 8, 2023, the Food and Drug Administration (FDA) approved Lyfgenia (lovotibeglogene autotemcel), indicated for treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events. Lyfgenia uses a lentiviral vector (LVV) to create a modified form of the β-globin gene ($\beta^{A\text{-}T87Q}$-globin) that produce functionally active hemoglobin containing βA-T87Q-globin (HbA^{T87Q}), a modified form of adult hemoglobin (HbA). Mechanistically, HbA^{T87Q} confers similar oxygen-binding affinity as HbA and also inhibits HbS polymerization thus limiting RBC sickling.[6]

Lyfgenia is administered as a single dose (once per lifetime) via intravenous infusion over less than 30 minutes with a single dose containing at minimum 3 x 10^6 CD34+ cells/kg of body weight. Prior to Lyfgenia administration, it must be confirmed that autologous hematopoietic stem cell (HSC) transplantation is appropriate for the patient. This includes screening for infectious diseases including, human immunodeficiency virus 1 & 2 (HIV-1/HIV-2), in accordance with clinical guidelines. Patients must then undergo mobilization and apheresis procedures, followed by myeloablative conditioning before receiving Lyfgenia.[6]

FDA approval was based on results from the Phase I/II (HGB-206, Cohort C), single-arm, 24-month, open-label study. Patients were included between the ages of 12 and 50 years with a diagnosis of sickle cell disease with either βS/βS or βS/β0 or βS/β+ genotype and clinically stable Karnofsky performance status of ≥ 60 (for patients ≥ 16 years of age) or a Lansky performance status of ≥ 60 (for patients < 16 years of age). Additionally, patients had to have failed or had intolerance to hydroxyurea and experienced at least four severe vaso-occlusive events (VOEs) in the 24 months before enrollment. Individuals were ineligible for the trial if they had a willing, matched HLA-identical sibling hematopoietic cell donor. Additional exclusions of note are active infection, advanced liver disease, history of severe cerebral vasculopathies, inadequate bone marrow function, contraindications to mobilization and myeloablative conditioning medicinal products, malignancy or immunodeficiency disorder, prior allogeneic transplant receipt.[6,7]

The primary efficacy endpoint was complete resolution of VOEs and severe VOEs between 6-18 months after infusion. A total of 36 participants received an infusion of Lyfgenia with 32 participants evaluated for the primary endpoint. Primary efficacy results demonstrated 88% (n=28/32) of participants had a complete resolution of VOEs with 94% (n=30/32) experiencing complete resolution of severe VOEs. A total of 4 of the 21 patients who achieved complete resolution of VOEs, went on to experience a VOE after the primary evaluation period to last follow-up. Globin response (GR) was achieved and maintained in 86% (31/36) patients. Of note, 49% (17/35) of patients were prescribed opioids for sickle cell and non-sickle cell-related pain after the primary evaluation period up to 24 months.[6]

From a safety perspective, Lyfgenia carries a boxed warning related to hematologic malignancy and requires patients be monitored closely through complete blood counts at least every 6 months and through integration site analysis at months 6, 12, and as needed. Two patients treated with an earlier version of Lyfgenia, that used a different manufacturing process than the marketed version, developed acute myeloid leukemia. One patient with α-thalassemia trait was diagnosed with myelodysplastic syndrome (MDS). Lyfgenia has not been studied in individuals with more than two α-globin gene deletions. Warnings and precautions include delayed platelet engraftment, neutrophile engraftment failure, insertional oncogenesis, hypersensitivity reactions, anti-retroviral use, hydroxyurea use, iron chelation, and PCR-based testing interference. Most common adverse included stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia.[6]

Other Gene Therapies in SCD

In addition to Lyfgenia, a second gene therapy, Casgevy (exagamglogene autotemcel) was also FDA approved on December 8, 2023, for treatment of patients aged 12 years and older with sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs). Casgevy's indication was later expanded to include treatment of transfusion-dependent β-thalassemia (TDT) and further expanded to include patients 2 years older for both SCD and TDT.[8] **[See Casgevy-exagamglogene autotemcel (Pharmacy-120)].** In August 2023, The Institute for Clinical and Economic Review (ICER) published a Final Evidence Report on sickle cell disease gene therapies. Majority of the panelists found the current evidence adequate to demonstrate a net health benefit for Lyfgenia and Casgevy when compared to

standard of care. When comparing Lyfgenia to Casgevy, ICER noted there was inadequate evidence to distinguish a benefit of one therapy over another.[9]

POLICY:

Lyfgenia (lovotibeglogene autotemcel) - Medical
1. Must be prescribed by a Hematologist or prescriber who specializes in management of sickle cell disease (SCD) **AND** 2. Must be ≥ 12 of age **AND** 3. Must have documentation of **all** the following (a-d): a. Patient has a confirmed diagnosis of sickle-cell disease with one of the following βS/βS or βS/β0 or βS/β+ genotype. Additional genotypes will be considered on a case-by-case basis based on disease severity **AND** b. History of at least 2 severe vaso-occlusive events or crises (VOCs/VOEs) per year over the last 2 years. Severe VOC/VOE is defined as at least **ONE** of the following (i, ii, iii, or iv): i. Acute pain episode that requires a visit to a medical facility and administration of pain medications (opioids or IV NSAIDs) or RBC transfusions **OR** ii. Acute chest syndrome (ACS), as indicated by presence of new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever **OR** iii. Hepatic sequestration **OR** iv. Priapism lasting more than 2 hours and leading to a medical facility visit **AND** c. Must have experienced **ONE** of the following pertaining to hydroxyurea (i, ii, or iii): i. A therapeutic failure (ex. continued frequent and/or severe VOCs or ongoing, frequent transfusion requirements) to a ≥ 6 consecutive month trial of hydroxyurea at maximum tolerated dosing. Adherence will be assess based on: 1. Pharmacy refill history. If the patient does not have pharmacy benefits through this health plan, a recent pharmacy profile will be requested. Progress notes documenting usage of sample medication may also be requested **OR** ii. A contraindication to hydroxyurea defined as a hypersensitivity to hydroxyurea or any component of the formulation **OR** iii. Must have experienced two hematologic toxicity reactions with hydroxyurea that resulted in discontinuation of therapy 1. Hematologic toxicity with hydroxyurea is defined by neutrophil, platelet, hemoglobin and/or reticulocyte count abnormalities concurrent with hydroxyurea use suggestive of hematologic toxicity. After the first hematologic toxicity, hydroxyurea therapy should be stopped and can be restarted with a dose reduction upon hematologic recovery. If a second hematologic toxicity is experienced, treatment should be discontinued **AND** d. Must have a Karnofsky performance status of at least 60 (for patients ≥16 years of age) or a Lansky performance status of at least 60 (for those <16 years of age) **AND** 4. Must be used as a single agent therapy (not applicable to myeloablative conditioning therapy) **AND** 5. The patient must be eligible to undergo hematopoietic stem cell transplant (HSCT) **AND** 6. Patient has been screened and found negative for active infections of the following: hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus 1 &2 (HIV-1/HIV-2) in accordance with clinical guidelines prior to collection of cells (documentation of laboratory results taken within the past 3 months is required) **AND** 7. Patient will not receive concomitant therapy with any of the following: a. Hydroxyurea for at least 2 months prior to mobilization and until all cycles of apheresis are completed **AND** b. Disease-modifying agents (e.g., L-glutamine, voxelotor, crizanlizumab) for at least 2 months prior to mobilization **AND**

8. Prescriber must attest that the patient will not be re-started on hydroxyurea or other disease modifying therapies for SCD after receipt of Lyfgenia **AND**
9. Patients with **ANY** of the following will not be eligible for coverage:
   a. An accessible and willing 10/10 human leukocyte antigen (HLA)-matched related donor
   b. Prior treatment with an allogeneic stem cell transplant
   c. Prior treatment with gene therapy/editing product
   d. Clinically significant and active bacterial, viral, fungal, or parasitic infection
   e. History of severe cerebral vasculopathy: defined by overt or hemorrhagic stroke; abnormal transcranial Doppler [≥200 cm/sec] needing chronic transfusion; or occlusion or stenosis in the polygon of Willis; or presence of Moyamoya disease
   f. Advanced liver disease, defined as any of the following:
      i. Persistent aspartate transaminase, alanine transaminase, or direct bilirubin value >3× the upper limit of normal (ULN)
      ii. Baseline prothrombin time or partial thromboplastin time >1.5× ULN.
      iii. History of cirrhosis or any evidence of bridging fibrosis, or active hepatitis
   g. Baseline creatinine clearance ≤ 70 mL/min/1.73 m^2 (documentation of laboratory results taken within the past 3 months is required)
   h. Any contraindications to the use of plerixafor during the mobilization of hematopoietic stem cells and any contraindications to the use of busulfan and any other medicinal products required during the myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients
   i. History of prior or current malignancy or immunodeficiency disorder, except previously treated, non-life threatening, cured tumors such as squamous cell carcinoma of the skin
   j. An immediate family member with a known or suspected Familial Cancer Syndrome
   k. Two or more α-globin gene deletions (documentation of results are required)
10. Lyfgenia is indicated for one-time single-dose intravenous use only and therefore will not be authorized for retreatment. Retreatment will be considered Experimental/Investigational when any FDA approved gene therapy, or any other gene therapy under investigation, has been previously administered
11. The minimum recommended dose of Lyfgenia is 3 × 10^6 CD34+ cells/kg
    a. Please refer to Lyfgenia FDA-approve prescribing information for complete dosage and administration instructions
    b. Lyfgenia is for autologous use only
12. Lyfgenia (lovotibeglogene autotemcel) is considered investigational when the above criteria are not met.
13. Lyfgenia (lovotibeglogene autotemcel) is considered investigational for all other indications.
14. **All requests for sickle cell gene therapy will require treatment with Casgevy. This does not apply to MMC/HARP.**
15. Authorization will be for 6 months to allow sufficient time for administration.

POLICY GUIDELINES:

1. Utilization Management is contract dependent. Refer to specific contract/benefit language for exclusions.
   a. Coverage criteria may be dependent on the contract renewal date.
   b. Coverage of drugs listed in this policy are contract dependent.
   c. Not all contracts/benefits allow coverage of healthcare professional administered drugs as part of their pharmacy benefit
   d. Not all contracts/benefits cover all medical infusible drugs.

2. This policy does not apply to Medicare Part D and D-SNP pharmacy benefits. The drugs in this policy may apply to all other lines of business including Medicare Advantage.
3. For members with Medicare Advantage, medications with a National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) will be covered pursuant to the criteria outlined by the NCD and/or LCD. NCDs/LCDs for applicable medications can be found on the CMS website at https://www.cms.gov/medicare-coverage-database/search.aspx. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS permits a Medicare Advantage Organization (MAO) to establish its own coverage determinations in accordance with 42 CFR § 422.101(b)(6). Indications that have not been addressed by the applicable medication's LCD/NCD will be covered in accordance with criteria determined by the Health Plan. Step therapy requirements may be imposed in addition to LCD/NCD requirements.
4. Clinical documentation must be submitted for each request (initial and recertification [if applicable]) unless otherwise specified (e.g., provider attestation required). Supporting documentation includes, but is not limited to, progress notes documenting previous treatments and treatment history, diagnostic testing, laboratory test results, genetic testing or biomarker results, imaging, and other objective or subjective measures of clinical benefit. Requested dosing must remain consistent with FDA-approved dosing recommendations.
5. All utilization management requirements outlined in this policy are compliant with applicable New York State insurance laws and regulations. Policies will be reviewed and updated as necessary to ensure ongoing compliance with all state and federally mandated coverage requirements.
6. Effective January 1st, 2026, Lyfgenia will be reimbursed by the NYS Medicaid fee-for-service (FFS) program for MMC/HARP members. The prior authorization process for these medications will remain unchanged. The Plan will continue to review these medications for medical necessity. New York State Medicaid Update - October 2025 Volume 41 - Number 10
7. Manufacturers may either discontinue participation in, or may not participate in, the Medicaid Drug Rebate Program (MDRP). Under New York State Medicaid requirements, physician-administered drugs must be produced by manufacturers that participate in the MDRP. Products made by manufacturers that do not participate in the MDRP will not be covered under Medicaid Managed Care/HARP lines of business. Drug coverage will not be available for any product from a non-participating manufacturer. For a complete list of New/Reinstated & Terminated Labelers please visit: https://www.medicaid.gov/medicaid/prescriptiondrugs/medicaid-drug-rebate-program/newreinstated-terminated-labeler-information/index.html
8. The requested site of care may impact approval timeframe and is subject to review.
9. Unless otherwise indicated within drug specific criteria, the drugs listed in this policy are administered by a healthcare professional and therefore are covered under the medical benefit.
10. This policy is subject to ongoing revision. Newly marketed drugs and existing drugs with new indications may be subject to prior authorization until formal coverage criteria are established. Inclusion of a drug in this policy does not guarantee its current availability on the market, as some agents may be discontinued, withdrawn, or otherwise unavailable. As product status changes, drugs may be removed from the policy.
11. This policy is based on available evidence as of the last review date. Coverage determinations are subject to applicable plan documents, state and federal regulations, and individual patient circumstances. This policy does not constitute medical advice.
12. For commercial contracts, medical necessity determinations align with the Certificate of Coverage issued by the Health Plan, which states that covered services must be clinically appropriate and not primarily for the convenience of the member, the member's family, or the provider.
13. The following applies to all gene and cellular therapies unless otherwise specified within the drug-specific coverage criteria:
    a. Administration, Retreatment, and Treatment with Additional or Other Gene/Cellular Therapies

i. One-Time Administration
   1. Most gene and cellular therapies, whether autologous, allogeneic ("off-the-shelf"), or in vivo gene-transfer therapies, are designed and studied as one-time treatments.
   2. Repeat dosing, reinfusion, or sequential therapy with other gene or cellular products has not been established as safe, effective, or clinically appropriate.

ii. Retreatment/Repeat Administration
   1. Retreatment with the same gene or cellular therapy product is considered experimental and investigational because:
      a. Clinical trials evaluated these therapies as single-administration interventions
      b. Safety, efficacy, and durability of a second administration have not been established
      c. Risks of immune activation, insertional mutagenesis, or vector immunity may be increased with repeat dosing

iii. Treatment with an Additional or Other Gene/Cellular Therapy
   1. Treatment with an additional or different gene or cellular therapy after prior exposure to any gene or cellular therapy is currently considered experimental and investigational as there is lack of evidence demonstrating the following (a-c):
      a. Anticipated clinical benefit beyond available standard therapies
      b. Safety of sequential administration
      c. Justification for selecting a second gene/cellular intervention after a prior one
   2. This includes, but is not limited to:
      a. Switching between CAR-T products (e.g., CD19 → CD19 or CD19 → BCMA)
      b. Switching between autologous and allogeneic cellular therapies
      c. Sequential use of CAR-T, TCR-T, NK-cell therapies, or other genetically engineered cell therapies
      d. Receiving a gene therapy after previous gene or cellular therapy exposure
      e. Receiving an in vivo gene therapy following any prior vector-based therapy

iv. Prior Gene/Cell Therapy Exposure
   1. An individual is generally not eligible for additional gene or cellular therapy if they have previously received:
      a. Any autologous cellular therapy (e.g., CAR-T, TCR-T, TIL),
      b. Any allogeneic genetically modified cellular therapy,
      c. Any in vivo gene therapy (e.g., AAV, lentiviral vector)
      d. Any ex vivo gene-modified cell product
      e. Are being considered for any other gene or cellular therapy without documented evidence supporting safety and anticipated benefit.

CODES:

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key:
Experimental/Investigational = (E/I),
Not medically necessary/ appropriate = (NMN).
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UPDATES:

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