



MASSACHUSETTS

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Medical Policy

Gene Therapies for Sickle Cell Disease

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Related Policies

- Prior Authorization Request Form for Casgevy - Gene Therapies for Sickle Cell Disease, #[055](#)
- Prior Authorization Request Form for Lyfgenia - Gene Therapies for Sickle Cell Disease, #[079](#)

Policy

**Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members**

Exagamglogene autotemcel (Casgevy™)

Exagamglogene autotemcel (Casgevy™) may be considered **MEDICALLY NECESSARY** and may be covered for individuals with sickle cell disease when **ALL** the following criteria are met:

1. At least 12 years of age; **AND**
2. Must have documented genetic test confirming diagnosis of sickle cell disease with genotype of $\beta S/\beta S$, $\beta S/\beta 0$, $\beta S/\beta +$. Additional genotypes will be considered on an Individual Consideration (IC) basis based on disease severity.
3. Have a history of at least 4 severe vaso-occlusive crises in the past 24 months; **AND**
4. Does not have a known 10/10 human leukocyte antigen-matched related donor willing to participate in an allogeneic HSCT; **AND**
5. Has no history of receiving allogeneic hematopoietic stem cell transplant; **AND**
6. Does not have advanced liver disease; **AND**
7. Have a negative serologic test for HIV infection; **AND**
8. Have no active bacterial, fungal, parasitic, or viral infection, including active/uncontrolled HBV and HCV; **AND**
9. Have no history of receiving gene therapy or under consideration for treatment with another gene therapy for sickle cell disease

Exagamglogene autotemcel (Casgevy™) is considered **INVESTIGATIONAL** when the above criteria are not met.

Exagamglogene autotemcel (Casgevy™) is considered **INVESTIGATIONAL** for all other indications.

Repeat treatment of exagamglogene autotemcel is considered [INVESTIGATIONAL](#).

Lovotibeglogene autotemcel (Lyfgenia™)

Lovotibeglogene autotemcel (Lyfgenia™) may be considered [MEDICALLY NECESSARY](#) and may be covered for individuals with sickle cell disease when **ALL** the following criteria are met:

1. Are at least 12 years of age; **AND**
2. Diagnosis of sickle cell disease confirmed by genetic testing demonstrating the following:
 - a. Homozygous sickle cell disease (e.g., HbSS); **OR**
 - b. Heterozygous sickle cell disease (e.g., HbSC, HbSβ⁺, HbSβ⁰, HbSD, HbSOArab, HbSE); **AND**
3. Documented history of one of the following clinical signs or symptoms in the last 12 months in the setting of appropriate supportive care measures for sickle cell disease (e.g., pain management plan):
 - a. Acute pain event requiring a visit to a medical facility and administration of pain medications (e.g. opioids (IV or oral), or intravenous non-steroidal anti-inflammatory drugs), hydration therapy, or red blood cell transfusions
 - b. Acute chest syndrome
 - c. Acute hepatic sequestration
 - d. Acute splenic sequestration
 - e. Priapism lasting > 2 hours and requiring a visit to a medical facility; **AND**
4. Meet the institutional requirements for a stem cell transplant procedure where the individual is expected to receive gene therapy (see Policy Guidelines). These requirements may include:
 - a. Adequate Karnofsky performance status or Lansky performance status;
 - b. Absence of advanced liver disease;
 - c. Adequate estimate glomerular filtration rate (eGFR);
 - d. Adequate diffusing capacity of the lungs for carbon monoxide (DLCO);
 - e. Adequate left ventricular ejection fraction (LVEF);
 - f. Absence of clinically significant active infection(s); **AND**
5. Have not received a previous allogeneic hematopoietic stem cell transplant; **AND**
6. Have not received any gene therapy or are under consideration for treatment for another gene therapy for sickle cell disease.

Lovotibeglogene autotemcel is considered [INVESTIGATIONAL](#) when the above criteria are not met.

Lovotibeglogene autotemcel is considered [INVESTIGATIONAL](#) for all other indications.

Repeat treatment with lovotibeglogene autotemcel is considered [INVESTIGATIONAL](#).

Policy Guidelines

Recommended Dose: The minimum dose is 3×10^6 CD34⁺ cells/kg.

Dosing Limits: 1 injection per lifetime

Clinical Requirements for a Stem Cell Transplant:

The requirement for eligibility for a stem cell transplant varied between the pivotal trial for exagamglogene autotemcel and lovotibeglogene autotemcel. These requirements are summarized below:

- Adequate cell counts defined as WBC < $3 \times 10^9/L$, ANC < $1 \times 10^9/L$ (< $0.5 \times 10^9/L$ for those on hydroxyurea treatment), or platelets < 50 to $100 \times 10^9/L$
- Adequate hear function defined as LVEF < 45% or cardiac T2* < 10 ms
- Advanced liver disease as defined as ALT > 3x ULN, direct bilirubin value > 2x ULN, PT INR > 1.5x ULN, history of cirrhosis or any evidence of bridging fibrosis, or active hepatitis on liver

- biopsy
- Adequate lung function defined as DLCO < 50% of predicted value and baseline oxygen saturation < 90% without supplemental oxygen
- Adequate performance status defined as Karnofsky performance status > 60 (≥ 16 years of age) or Lansky performance status > 60 (< 16 years of age)
- Adequate kidney function as defined as eGFR < 60 to 70 mL/min/1.73 m²

Other Considerations:

There is a boxed warning for hematologic malignancy for lovotibeglogene autotemcel. Hematologic malignancy has occurred in patients treated with lovotibeglogene autotemcel. It is recommended to monitor treated individuals closely for evidence of malignancy through complete blood counts at least every 6 months for at least 15 years after treatment and through integration site analysis at months 6, 12, and as warranted.

Drug-drug interactions between iron chelators and the myeloablative conditioning agent must be considered. Iron chelators should be discontinued at least 7 days prior to initiation of conditioning. Some iron chelators are myelosuppressive. It is recommended to avoid use of non-myelosuppressive iron chelators for at least 3 months and use of myelosuppressive iron chelators for at least 6 months after the infusion of exagamglogene autotemcel or lovotibeglogene autotemcel. Phlebotomy can be used in lieu of iron chelation, when appropriate.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is required .
Commercial PPO and Indemnity	Prior authorization is required .
Medicare HMO BlueSM	Prior authorization is required .
Medicare PPO BlueSM	Prior authorization is required .

Requesting Prior Authorization Using Authorization Manager

Providers will need to use [Authorization Manager](#) to submit initial authorization requests for services. Authorization Manager, available 24/7, is the quickest way to review authorization requirements, request authorizations, submit clinical documentation, check existing case status, and view/print the decision letter. For commercial members, the requests must meet medical policy guidelines.

To ensure the request is processed accurately and quickly:

- Enter the facility’s NPI or provider ID for where services are being performed.
- Enter the appropriate surgeon’s NPI or provider ID as the servicing provider, *not* the billing group.

Authorization Manager Resources

- Refer to our [Authorization Manager](#) page for tips, guides, and video demonstrations.

Complete Prior Authorization Request Form for Gene Therapies using [Authorization Manager](#) for:

- Exagamglogene autotemcel (Casgevy™), ([#055](#))
- Lyfgenia™ (Lovotibeglogene autotemcel), ([#079](#))

For out of network providers: Requests should still be faxed to 888-973-0726.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

HCPCS Codes

HCPCS codes:	Code Description
C9399	Unclassified drugs or biologicals
J3394	Injection, lovotibeglogene autotemcel, per treatment
J3490	Unclassified drugs
J3590	Unclassified biologics

ICD-10 Procedure Codes

ICD-10 PCS Procedure Codes	Code Description
XW143H9	Transfusion of Lovotibeglogene Autotemcel into Central Vein, Percutaneous Approach, New Technology Group 9
XW143J8	Transfusion of Exagamglogene Autotemcel into Central Vein, Percutaneous Approach, New Technology Group 8

Description

Sickle Cell Disease (SCD)

Sickle cell disease is a genetic disorder characterized by the presence of hemoglobin S (HbS) that includes, either from homozygosity for the sickle variant in the beta globin chain of hemoglobin (β^S/β^S) or from compound heterozygosity of a sickle beta globin mutation with another beta globin mutation (eg, sickle-beta thalassemia such as β^S/β^0 or β^S/β^+ genotype). The homozygous form (β^S/β^S) accounts for 60% to 70% of sickle cell disease in the United States.¹

Production of hemoglobin with dysfunctional hemoglobin S forms polymers in the red blood cells of patients. Among healthy individuals, red blood cells are flexible and round allowing them to move easily through blood vessels. With sickle cell disease, those red blood cells are sickled or shaped like crescent moons causing them to slow down or cause blockage as blood flows through the blood vessels. This results in vascular obstruction and ischemia; a shortened lifespan of the red blood cells leading to both intravascular and extravascular hemolysis, and a sticky red blood cells surface increases adherence to the vascular endothelium which can result in vascular obstruction and can contribute to vascular proliferative lesions.² Recurrent acute pain crises, or vaso-occlusive crises, are the most prevalent manifestations of sickle cell disease.³ Patients also experience acute complications including serious infections and non-infectious complications such as stroke, renal necrosis, and priapism.⁴ Acute chest syndrome is a potentially life-threatening complication that can involve chest pain and shortness of breath among other symptoms.⁵ Chronic complications can emerge across multiple organs and include delayed puberty, avascular necrosis, skin ulcers, chronic pain, neurocognitive impairment, chronic kidney injury, pulmonary hypertension, cardiovascular disease, and can result in early mortality.⁴

Incidence and prevalence of sickle cell disease vary considerably by geography with the highest rates in equatorial Africa, Brazil, Saudi Arabia and central India populations.⁶ It is estimated that there are approximately 100,000 individuals living with sickle cell disease in the United States.⁷

As of 2008, screening for sickle cell disease in newborns is mandated in all 50 states of the United States and the District of Columbia, regardless of birth setting.⁸ The diagnostic methods used after birth are those that separate hemoglobin species according to amino acid composition (hemoglobin electrophoresis or thin layer isoelectric focusing), solubility testing, and examination of the peripheral blood smear.¹

Current Treatment

Specific interventions for sickle cell disease include stem cell transplantation, chronic transfusion with packed red blood cells, and hydroxyurea. While stem cell transplant can be curative, the degree of myeloablation required and lack of availability of matched donors limit its use. Chronic transfusion is generally used for primary or secondary stroke prevention. Hydroxyurea is used to reduce the number of acute pain crises in those with frequent or severe crises, and in those with a history of acute chest syndrome or severe anemia.³ Hydroxyurea improves blood flow by decreasing sickling of red blood cells and altering the adhesion of red blood cells to endothelium. Also, it increases red blood cells survival and decreases white blood cell, reticulocyte and platelet counts.¹ Acute pain crisis may be managed with pain medications including opioids, and may require additional inpatient or outpatient treatments including hydration, transfusion, supplemental oxygen, and a variety of other treatments.³

In recent years, multiple specific disease-modifying treatments have been approved by the FDA for treatment of complications resulting from sickle cell disease. L-glutamine supplementation is used to decrease the frequency of acute pain crises.⁹ It was approved by the FDA on July 7, 2017 to reduce the acute complications of sickle cell disease in adult and pediatric individuals 5 years of age and older.

Crizanlizumab is a humanized monoclonal antibody that binds to P-selectin.¹⁰ It was approved by the FDA on November 15, 2019 to reduce the frequency of vaso-occlusive crises in adults and pediatric individuals aged 16 years and older with sickle cell disease. It is administered intravenously in 2 loading doses 2 weeks apart and then every 4 weeks thereafter. Voxelotor is an HbS polymerization inhibitor that reversibly binds to hemoglobin to stabilize the oxygenated hemoglobin state, thus shifting the oxyhemoglobin dissociation curve.¹¹ Voxelotor was approved by the FDA on November 25, 2019 for the treatment of sickle cell disease in adults and pediatric individuals 12 years of age and older.

Summary of Evidence

Exagamglogene autotemcel (Casgevy™)

The safety and efficacy of exa-cel (exagamglogene autotemcel) was evaluated in the CLIMB-THAL III trial, for treatment of transfusion-dependent β -thalassemia (TDT). Pharmacokinetic-adjusted busulfan myeloablation followed by Casgevy infusion was administered to eligible participants 12 to 35 years of age with TDT and history of significant transfusion dependence.

Primary Endpoint:

Proportion of individuals achieving a maintained weighted average hemoglobin (Hb) ≥ 9 g/dL without red blood cell (RBC) transfusion for ≥ 12 months after Casgevy infusion, starting 60 days after their last RBC transfusion.

Results:

Results showed that 42 out of 44 individuals stopped RBC transfusions. Median time from the last transfusion was 9 months. Increases in fetal hemoglobin (HbF) and mean total Hb levels (>9 g/dL)

were achieved by Month 3. The mean total Hb levels increased to and was maintained at >11 g/dL after 3 months. In all individuals with ≥1 year of follow-up, the mean proportion of edited BCL11A alleles in bone marrow CD34+ hematopoietic stem and progenitor cells (HSPCs) and peripheral blood mononuclear cells was 74.3% and 63.4%, respectively, at Month 6 and remained stable. For participants who had at least a 12-month follow-up, 16 out of 17 were free of severe VOCs.

Adverse Events (AEs) and Serious Adverse Events (SAEs):

- 34% reported AEs with 40% reported as SAEs
- 2 Participants with SAEs considered related to Casgevy
- All SAEs resolved with no reported deaths, discontinuation or malignancies

Safety: Safety profile was comparable to busulfan myeloablation and autologous transplant. There was one death attributed to SAR-CoV-2 infection potentially due to pulmonary compromise from busulfan and one participant required therapeutic phlebotomy. Off-Target genome editing was not observed in the edited CD34+ cells evaluated from healthy donors and treated individuals. However, the risk of unintended, off-target editing in an individual's CD34+ cells cannot be ruled out due to genetic variants. The clinical significance of potential off-target editing is unknown. Neutrophil engraftment failure is a potential risk, defined as not achieving neutrophil engraftment after exagamglogene autotemcel infusion and requiring use of unmodified rescue CD34+ cells and all participants treated during the trial achieved neutrophil engraftment with no need for rescue CD34+ cells. Longer median platelet engraftment times were observed with exagamglogene autotemcel treatment compared to allogeneic HSC transplant. There is an increased risk of bleeding until platelet engraftment is achieved. It is recommended to monitor for bleeding according to standard guidelines and medical judgment. It is recommended that hydroxyurea, voxelotor, and/or crizanlizumab be discontinued at least 8 weeks prior to the start of mobilization and conditioning as their interaction with exagamglogene autotemcel, mobilization, and myeloablative conditioning are unknown. Drug-drug interactions between iron chelators and the myeloablative conditioning agent must be considered. Iron chelators should be discontinued at least 7 days prior to initiation of conditioning. Some iron chelators are myelosuppressive. After exagamglogene autotemcel infusion, avoid use of non-myelosuppressive iron chelators for at least 3 months and use of myelosuppressive iron chelators for at least 6 months. Phlebotomy can be used in lieu of iron chelation, when appropriate.

Conclusion: Casgevy infusion led to the elimination of transfusions in almost all individuals with TDT across all genotypes included in the study, with clinically meaningful increases in HbF and total Hb levels.

Lovotibeglogene autotemcel (Lyfgenia™)

In the pivotal HGB-206 (Group-C) study, a total of 36 study participants received a single intravenous infusion of lovotibeglogene autotemcel. Of the 36 total participants, 32 study participants were evaluable for the endpoints of complete resolution of VOEs and sVOEs in the 6 to 18 months post-infusion including 8 adolescent study participants. Severe VOEs were eliminated for 94% (30/32) of evaluable study participants and all VOEs were eliminated for 88% (28/32) of evaluable study participants between 6 - and 18-months post-infusion. Safety data includes data from 54 study participants who initiated stem cell collection. Three cases of hematologic malignancy (2 cases of acute myeloid leukemia and 1 case of myelodysplastic syndrome) were reported in the pivotal trial. As per the prescribing label, individuals treated with lovotibeglogene autotemcel should have lifelong monitoring for hematologic malignancies with a complete blood count (with differential) at least every 6 months for at least 15 years after treatment, and integration site analysis at months 6, 12, and as warranted. Other adverse reactions were related to myeloablative conditioning or underlying disease. In addition to a limited sample size, the length of follow-up is not long enough to remove uncertainty regarding the durability of effect over a longer time period.

After the primary evaluation period to last follow-up, 4 of 32 study participants who achieved VOE-

CR experienced VOs while maintaining globin response. After the primary evaluation period up to 24 months, 17 of 35 (49%) study participants were prescribed opioids for sickle cell and non-sickle cell-related pain. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect as well as side effects. The limited sample sizes of the studies create uncertainty around the estimates of some of the patient-important outcomes, particularly adverse events. Some serious harms are likely rare occurrences and as such may not be observed in trials. While most of the serious adverse events were attributable to known risks associated with myeloablative conditioning, uncertainty remains about the degree of risk of insertional oncogenesis with lovotibeglogene autotemcel in real-world practice.

Policy History

Date	Action
7/2024	Clarified coding information.
5/2024	Policy clarified. Updated criteria for history of supportive care measures to include additional examples of pain medications for an acute pain event.
4/2024	Policy revised. Lovotibeglogene autotemcel (Lyfgenia) is considered medically necessary for treatment of individuals with sickle cell disease who meet criteria. Effective 4/1/2024.
3/2024	Clarified genotype coding and leukocyte antigen-matched criteria.
1/2024	New medical policy describing medically necessary and investigational indications for Casgevy. Effective 1/1/2024. New medical policy describing non-covered status for Lyfgenia. Effective 1/1/2024.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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