LifeWise
Health Plan of Washington

PHARMACY / MEDICAL POLICY – 5.01.640

Pharmacologic Treatment of Sickle Cell Disease

Effective Date:	Feb. 1, 2024	RELATED MEDICAL POLICIES:
Last Revised:	Jan. 1, 2025	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Sickle cell disease (SCD) is a genetic condition where red blood cells develop an abnormal shape like a sickle which affects their ability to carry oxygen effectively. This sickled shape causes the cells to stick together, leading to blockages in blood vessels and disrupting blood flow. SCD can lead to various symptoms, including severe pain known as pain crises or vaso-occlusive crises, anemia, infections, and damage to organs like the spleen, liver, and kidneys. Severity of symptoms can vary widely among individuals. Some may experience mild symptoms, while others can have frequent crises and significant health complications.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those age 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based

outpatient setting, an infusion center, a physician's office, or at home. Click **here** to be directed to the site of service review criteria.

Drugs subject to site of service review addressed in this policy are:

- Adakveo (crizanlizumab-tmca)

Site of Service Administration	Medical Necessity
Medically necessary sites of service • **Physician's office** • **Infusion center** • **Home infusion**	**IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site:** • These are the preferred **medically necessary** sites of service for specified drugs.
Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.** **This site is considered medically necessary for the first 90 days for the following:** • The initial course of infusion of a pharmacologic or biologic agent **OR** • Re-initiation of an agent after 6 months or longer following discontinuation of therapy* **Note:** *This does not include when standard dosing between infusions is 6 months or longer **This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the individual's home and there is no contracted home infusion agency that**

Site of Service Administration	Medical Necessity
	will travel to their home, or a hospital is the only place that offers infusions of this drug. **This site is considered medically necessary only when the individual has a clinical condition which puts him or her at increased risk of complications for infusions, including any ONE of the following:** • Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, %FVC ≤ 40%) that may increase the risk of an adverse reaction • Unstable renal function which decreases the ability to respond to fluids • Difficult or unstable vascular access • Acute mental status changes or cognitive conditions that impact the safety of infusion therapy • A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug
Hospital-based outpatient setting • **Outpatient hospital IV infusion department** • **Hospital-based outpatient clinical level of care**	**These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.**

Drug	Medical Necessity
Adakveo (crizanlizumab-tmca) IV	**Adakveo (crizanlizumab-tmca) IV is subject to review for site of service administration.** **Adakveo (crizanlizumab-tmca) may be considered medically necessary for the treatment of sickle cell disease when the following are met:**

Drug	Medical Necessity
	• The individual must be aged 16 years or older **AND** • Occurrence of 1 vaso-occlusive crisis (e.g., acute chest syndrome, hepatic sequestration, etc.) in the past 12 months **AND** • Concurrent use of or treatment failure with hydroxyurea **AND** • Is not on a planned blood transfusion therapy program **AND** • Not used in combination with Oxbryta **AND** • Adakveo (crizanlizumab-tmca) is prescribed by or in consultation with a hematologist **Initial approval will be for 12 months** **Re-authorization criteria:** • Continued therapy will be approved for 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by no increase in the number of vaso-occlusive events in 12 months compared to baseline.
Casgevy (exagamglogene autotemcel) IV	**Casgevy (exagamglogene autotemcel) may be considered medically necessary for the treatment of sickle cell disease when the following are met:** • The individual is aged 12 years or older **AND** • Has been diagnosed with sickle cell disease (SCD) **AND** • Has experienced at least 4 sickle-cell related events where supportive care measures were provided in the previous 24 months **AND**

Drug	Medical Necessity

	• Casgevy (exagamglogene autotemcel) is prescribed by or in consultation with a hematologist or transplant specialist
	AND
	• The individual does NOT have any of the following:
	  ○ The presence of Moyamoya disease
	  ○ Advanced liver disease defined as ONE or more of the following:
	  ▪ Clear evidence of liver cirrhosis, active hepatitis, or significant fibrosis
	  ▪ Liver iron concentration ≥15 mg/g unless liver biopsy shows no evidence of cirrhosis, active hepatitis, or significant fibrosis
	  ○ Presence of any of the following:
	  ▪ Human immunodeficiency virus type 1 or 2 infection (HIV-1 or HIV-2)
	  ▪ Hepatitis B virus (HBV) infection without either of the following:
	  ▫ Previous vaccination and negative markers of hepatitis B
	  ▫ Previous HBV exposure provided a negative for HBV DNA
	  ▪ Hepatitis C virus (HCV) infection or detectable hepatitis C viral load in individuals positive for HCV antibody
	  ○ Any prior or current malignancy (with the exception of non-melanoma skin cancers)
	  ○ History of receiving prior gene therapy or allogeneic transplant
	  ○ Contraindication to the use of plerixafor, busulfan, or any other medicinal products required during myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients

Endari (L-glutamine) oral	**Endari (L-glutamine) may be considered medically necessary to reduce acute complications of sickle cell disease when the following are met:**

Drug	Medical Necessity
	• The individual must be aged 5 years or older **AND** • Occurrence of 1 vaso-occlusive crisis (e.g., acute chest syndrome, hepatic sequestration, etc.) in the past 12 months **AND** • Concurrent use of or treatment failure with hydroxyurea **AND** • Endari (L-glutamine) is prescribed by or in consultation with a hematologist **AND** • The daily dose of Endari (L-glutamine) is ≤30 grams per day (taken twice daily) **Initial approval will be for 12 months.** **Re-authorization criteria:** • Continued therapy will be approved for 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by no increase in the number of vaso-occlusive events in 12 months compared to baseline.
Lyfgenia (lovotibeglogene autotemcel) IV	**Lyfgenia (lovotibeglogene autotemcel) may be considered medically necessary for the treatment of sickle cell disease when the following are met:** • The individual is aged between 12 years and 50 years of age **AND** • Has been diagnosed with sickle cell disease (SCD) **AND** • Has experienced at least 4 sickle-cell related events where supportive care measures were provided in the previous 24 months **AND**

Drug	Medical Necessity

	• Has a Karnofsky performance status of ≥60 for adults (≥16 years of age) or a Lansky performance status of ≥60 for adolescents (<16 years of age)
	AND
	• Has tried and failed or had an intolerance to hydroxyurea
	AND
	• Lyfgenia (lovotibeglogene autotemcel) is prescribed by or in consultation with a hematologist or transplant specialist
	AND
	• The individual does NOT have any of the following:
	  ○ An absolute neutrophil count of <1,000/µL (<500/µL for subjects on hydroxyurea treatment) or a platelet count <100,000/µL
	  ○ Severe cerebral vasculopathy, defined as ONE or more of the following:
	  ▪ Any history of overt ischemic or hemorrhagic stroke
	  ▪ >50% stenosis or occlusion in the circle of Willis
	  ▪ The presence of Moyamoya disease
	  ○ Advanced liver disease defined as ONE or more of the following:
	  ▪ Clear evidence of liver cirrhosis, active hepatitis, or significant fibrosis
	  ▪ Liver iron concentration ≥15 mg/g unless liver biopsy shows no evidence of cirrhosis, active hepatitis, or significant fibrosis
	  ○ Evidence of chronic kidney disease
	  ○ History of iron overload with cardiac T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec
	  ○ Clinically significant pulmonary hypertension at baseline
	  ○ Unable to receive red blood cell transfusions
	  ○ Presence of genetic mutations that result in the inactivation of 2 or more α-globin genes
	  ○ Presence of any of the following:

Drug	Medical Necessity
	▪ Human immunodeficiency virus type 1 or 2 infection (HIV-1 or HIV-2) ▪ Hepatitis B virus (HBV) infection without either of the following: ▫ Previous vaccination and negative markers of hepatitis B ▫ Previous HBV exposure provided a negative for HBV DNA ▪ Hepatitis C virus (HCV) infection or detectable hepatitis C viral load in individuals positive for HCV antibody ○ Any prior or current malignancy (with the exception of non-melanoma skin cancers) ○ Any immediate family member (i.e., parent or siblings) with a known or suspected Familial Cancer Syndrome (including but not limited to hereditary breast and ovarian cancer syndrome, hereditary nonpolyposis colorectal cancer syndrome, and familial adenomatous polyposis) ○ Any prior or current immunodeficiency disorder ○ History of receiving prior gene therapy or allogeneic transplant ○ Any contraindication to the use of plerixafor, busulfan, or any other medicinal products required during myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients
Oxbryta (voxelotor) oral	**Oxbryta (voxelotor) may be considered medically necessary for the treatment of sickle cell disease when the following are met:** • The individual must be aged 4 years or older **AND** • Occurrence of 1 vaso-occlusive event in 12 months **AND** • Baseline hemoglobin <10.5 g/dL **AND** • Serum ferritin is ≥25 ng/mL

Drug	Medical Necessity
	AND • Have not received blood transfusion therapy within the prior six weeks **AND** • Is not on a planned blood transfusion therapy program **AND** • Not used in combination with Adakveo (crizanlizumab-tmca) **AND** • Oxbryta (voxelotor) is prescribed by or in consultation with a hematologist **Initial approval will be for 12 months.** **Re-authorization criteria:** • Continued therapy will be approved for 12 months as long as the medical necessity criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by an increase in hemoglobin level of at least 1 g/dL from baseline.

Drug	Investigational
Adakveo (crizanlizumab-tmca), **Endari (L-glutamine),** **Oxbryta (voxelotor)**	**All other uses of Adakveo (crizanlizumab-tmca), Endari (L-glutamine), and Oxbryta (voxelotor) for conditions not outlined in this policy are considered investigational.**
Casgevy (exagamglogene autotemcel), **Lyfgenia (lovotibeglogene autotemcel)**	**All other uses of Casgevy (exagamglogene autotemcel) and Lyfgenia (lovotibeglogene autotemcel) for conditions not outlined in this policy are considered investigational.** **Repeat treatment of Casgevy (exagamglogene autotemcel) or Lyfgenia (lovotibeglogene autotemcel) is considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Adakveo (crizanlizumab-tmca) may be approved for up to 12 months.** **Casgevy (exagamglogene autotemcel) or Lyfgenia (lovotibeglogene autotemcel) may be approved as a one-time infusion.** **Endari (L-glutamine) and Oxbryta (voxelotor) may be approved for up to 12 months.**
Re-authorization criteria	**Future re-authorization of Adakveo (crizanlizumab-tmca), Endari (L-glutamine), and Oxbryta (voxelotor) may be approved for up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.** **Repeat treatment of Casgevy (exagamglogene autotemcel) or Lyfgenia (lovotibeglogene autotemcel) is considered investigational.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

Code	Description
HCPCS	

Code	Description
J0791	Injection, crizanlizumab-tmca, (Adakveo) 5 mg
J3392	Injection, exagamglogene autotemcel, per treatment (Casgevy) (new code effective 1/1/2025)
J3394	Injection, lovotibeglogene autotemcel, per treatment (Lyfgenia) (new code effective 7/1/2024)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Consideration of Age

Age limits specified in this policy are determined according to the U.S. Food and Drug Administration (FDA)-approved indications, where applicable.

For site of service for medical necessity the age described in this policy is 13 years of age or older. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home. The age criterion for site of service for medical necessity is based on the following: Pediatric individuals are not small adults. Pediatric individuals differ physiologically, developmentally, cognitively, and emotionally from adult individuals, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatrics unique physiology and psychology, site of service review is limited to individuals above the age of 13.

The ages listed in the policy statements are based on FDA labeling for each drug:

- Adakveo: The safety of Adakveo has not been established in individuals younger than 16 years of age.

- Casgevy: The safety of Casgevy has not been established in individuals younger than 12 years of age.
- Endari: The safety of Endari has not been established in individuals younger than 5 years of age.
- Lyfgenia: The safety of Lyfgenia has not been established in individuals younger than 12 years of age and individuals older than 50 years of age.
- Oxbryta: The safety of Oxbryta has not been established in individuals younger than 4 years of age.

Benefit Application

Pharmacy Benefit

Endari (L-glutamine) and Oxbryta (voxelotor) are managed through the pharmacy benefit.

Medical Benefit

Adakveo (crizanlizumab-tmca), Casgevy (exagamglogene autotemcel), and Lyfgenia (lovotibeglogene autotemcel) are managed through the medical benefit.

Evidence Review

Background on Sickle Cell Disease

Sickle cell disease (SCD) is an inherited blood disorder that affects hemoglobin, the molecule in red blood cells that delivers oxygen to cells throughout the body. People with this disorder have atypical hemoglobin molecules called hemoglobin S, which can distort red blood cells into a sickle, or crescent, shape. The hallmark of SCD is the sickling of red blood cells, which can become rigid and sticky, leading to blockages in blood flow, acute pain crises or vaso-occlusive

crises (VOCs), and potential damage to organs and tissues as individuals age. This sickling occurs because the abnormal hemoglobin S polymerizes under low oxygen conditions. SCD is most commonly seen in individuals of African, Mediterranean, Middle Eastern, and Indian descent. The most severe form of the disease, sickle cell anemia, results from inheriting two sickle cell genes, one from each parent.

Epidemiologically, SCD is a major global health concern. According to the World Health Organization (WHO), about 5% of the world's population carries trait genes for hemoglobin disorders, chiefly sickle cell disease and thalassemia. Approximately 300,000 babies are born with SCD each year, predominantly in sub-Saharan Africa. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that SCD affects approximately 100,000 Americans. The disease imposes a significant health burden, particularly in areas with limited access to comprehensive healthcare. For instance, in Africa, up to 90% of infants born with SCD will die before reaching adulthood. In higher resource settings, the life expectancy of individuals with SCD has improved significantly, yet the disease still results in a reduced average lifespan.

There is an unmet need in treating SCD not only because of limited treatment options but also due to the negative impact on individual's quality of life and productivity. Individuals report having to miss out on school, work and social gatherings due to frequent hospitalizations and blood transfusions. SCD individuals face discrimination, stigma and inadequate pain management, they are often mistreated and mislabeled as pain killer drug seekers. The economic impact of SCD includes lost wages from missed work due to monthly transfusion, high treatment costs, and mental health therapy.

Adakveo (crizanlizumab-tmca)

SUSTAIN is a double-blind, randomized, placebo-controlled, phase 2 trial where 198 individuals were assigned to receive a low-dose crizanlizumab (2.5 mg/kg), high-dose crizanlizumab (5 mg/kg) or placebo over 52 weeks. Regardless of concomitant hydroxyurea use, all individuals were included. Crizanlizumab significantly reduced the median annual rate of vaso-occlusive crises (VOCs) by 45.3% compared to placebo (1.63 vs 2.98). The range of VOCs for both the crizanlizumab and placebo groups ranged from 0 to 24 in each treatment arm. In a prespecified subgroup analysis of the per-protocol population, individuals who received at least 12 of the 14 scheduled infusions of crizanlizumab experienced a 52% reduction in VOCs compared to placebo (1.04 vs 2.18).

Serious adverse events were reported in 55 individuals, 17 in the high-dose group and 21 in the low-dose group. There were two serious adverse events that occurred at a greater frequency than placebo, pyrexia and influenza. Infusion-related reactions (IRRs) occurred in 2 (3%) individuals treated with crizanlizumab 5 mg/kg, mostly during the first and second infusions. Management of IRRs included various treatments such as acetaminophen, NSAIDs, opioids, antihistamines, intravenous fluids, and/or oxygen therapy. In cases of severe IRRs, discontinuation of infusion and initiation of appropriate medical care was advised, along with consideration of permanent discontinuation of crizanlizumab.

STAND trial, a phase 3 clinical trial, did not show a reduction in the yearly occurrence of painful VOCs leading to a medical visit with crizanlizumab compared to placebo. This was observed in individuals treated with crizanlizumab at both the approved 5.0 mg/kg dose and a higher 7.5 mg/kg dose. Preliminary results indicated no statistically significant difference between placebo and the two different dosages of crizanlizumab in reducing annualized rates of VOCs leading to a healthcare visit over the first year after randomization. The study showed that individuals treated with crizanlizumab had on average 2.5 painful crises leading to a healthcare visit over the first year of treatment, compared with 2.3 crises in the placebo group. The STAND study did not indicate new safety concerns with crizanlizumab. The overall safety profile of crizanlizumab remains consistent with the commercially available 5 mg/kg dose.

Casgevy (exagamglogene autotemcel)

The clinical trial NCT03655678, also known as CLIMB-THAL III, evaluated the efficacy and safety of exa-cel (exagamglogene autotemcel) in treating transfusion-dependent β-thalassemia (TDT). Eligible individuals, aged 12 to 35 years with TDT and a history of significant transfusion dependence, underwent pharmacokinetic-adjusted busulfan myeloablation followed by Casgevy infusion. The primary endpoint was the 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 showed that 42 out of 44 individuals stopped RBC transfusions, with the median time since the last transfusion being 9.0 months. Increases in fetal hemoglobin (HbF) and mean total Hb levels (>9 g/dL) were achieved by Month 3, with mean total Hb levels increasing to and maintained at >11 g/dL thereafter. 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, remaining stable in all individuals with ≥1 year of follow-up. The study concluded that Casgevy infusion led to the elimination of transfusions in almost all individuals with TDT across all genotypes, with clinically meaningful increases in HbF and total Hb levels. 16 out of 17 trail participants who had at least 12 months of follow-up were free of severe VOCs.

34.3% of individuals treated with Casgevy reported adverse events (AEs), of this 40% reported serious adverse events (SAEs). Two individuals experienced SAEs considered related to Casgevy, but all SAEs resolved without deaths, discontinuations, or malignancies. The safety profile was generally consistent with that of busulfan myeloablation and autologous transplant. There was one death attributed to SAR-CoV-2 infection and potentially related to busulfan lung injury and one individual 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. In the clinical trial, all treated individuals achieved neutrophil engraftment and no individuals received rescue CD34+ cells. It is recommended to monitor absolute neutrophil counts and manage infections according to standard guidelines and medical judgement. In the event of neutrophil engraftment failure, individuals should be infused with 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.

Endari (L-glutamine)

NCT01179217 is a multicenter, randomized, placebo-controlled, double-blind, phase 3 trial that randomly assigned 230 individuals in a 2:1 ratio to receive L-glutamine (0.3g/kg of body weight) or placebo. This trial aimed to reduce the incidence of pain crises in individuals with sickle cell anemia or sickle β0-thalassemia. Two-thirds of the individuals in both groups also received concomitant hydroxyurea therapy. Individuals in the L-glutamine group experienced significantly fewer pain crises compared to the placebo group, with a median of 3.0 versus 4.0, respectively. Hospitalization rates were lower in the L-glutamine group, with a median of 2.0 hospitalizations compared to 3.0 in the placebo group. In addition, the number of recurrent events of sickle cell-related pain crises over time was 25% lower in the treatment group than the placebo group. Over a 48-week period, children and adults with sickle cell anemia receiving oral L-glutamine therapy, either alone or with hydroxyurea, had fewer pain crises than those receiving a placebo, with or without hydroxyurea. The number of ED visits that did not result in a hospitalization did not differ between trial groups.

A greater proportion of individuals in the placebo group experienced adverse events than the treatment group, a similar pattern was seen for the severe adverse events (87.1% vs. 78.2%) Adverse effects like low-grade nausea, noncardiac chest pain, fatigue, and musculoskeletal pain were more frequent in the L-glutamine group compared to the placebo group. Two individuals died in the L-glutamine group due to sudden cardiac death which are not related to the treatment studied. Long-term safety data beyond a year is still unknown, but there are potential adverse effects associated.

Lyfgenia (lovotibeglogene autotemcel)

The clinical trial NCT04293185, also known as HGB-210, a Phase 3, non-randomized, open-label, multi-site, single-dose study that evaluated the efficacy and safety of Lyfgenia (lovotibeglogene autotemcel) in approximately 35 adults and pediatric subjects aged between 2 and 50 years with SCD. The intervention involves a single dose of a drug product manufactured with autologous

CD34+ hematopoietic stem cells. These cells are collected via plerixafor mobilization and apheresis and then transduced with the BB305 lentiviral vector (LVV) encoding the human beta-A-T87Q globin gene. The treatment is administered via intravenous infusion following myeloablative conditioning with busulfan. One of the primary outcome measures for this study is the proportion of subjects achieving complete resolution of vaso-occlusive events (VOEs) between 6- and 18-months post-drug product infusion.

Post-engraftment, median total hemoglobin increased from 8.5 g/dL to ≥12 g/dL from baseline to 12 months. Sickle hemoglobin (HbS) levels in all individuals were less than 60% of total hemoglobin. All evaluable individuals (n=25) had complete resolution of severe vaso-occlusive events (VOEs) through up to 36 months of follow-up, compared to a median of 3.5 per year in the 24 months before enrollment. There was a reduction in the total number of annual hospital admissions and days. Non-severe VOEs were only reported in small sample (n = 10) with 90% free of any VOE. Key hemolysis markers approached normal levels post-treatment. Lactate dehydrogenase and indirect bilirubin levels normalized, and reticulocyte counts and haptoglobin levels approached normal, suggesting reduced hemolysis. Lyfgenia showed a reduction in pain intensity, improvement in Health Utility Index, and improvement in the number of work hours missed and total number of weekly work hours from baseline throughout 36 months of follow-up.

100% of participants reported AEs, >50% of participants experienced a grade ≥3 adverse event of stomatitis, thrombocytopenia, and neutropenia. There was one death in the Group C cohort 20 months post-infusion, the cardiac fibrosis was deemed unrelated to Lyfgenia. There were two deaths in Group A related to hematologic malignancy in the earlier cohort with no evidence of oncogenic insertion. There were two cases of suspected myelodysplastic syndromes (MDS), determined to be anemia from co-occurring alpha-thalassemia function.

There is a limitation of use for lovotibeglogene autotemcel in individuals with α-thalassemia trait (-α3.7/-α3.7) per the FDA label. These individuals may experience anemia with erythroid dysplasia that may require chronic red blood cell transfusions. Lovotibeglogene autotemcel has not been studied in individuals with more than two α-globin gene deletions.

There is a black box warning for hematologic malignancy. Hematologic malignancy has occurred in individuals 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.

Delayed platelet engraftment has been observed with lovotibeglogene autotemcel. It is recommended to monitor treated individuals for thrombocytopenia and bleeding according to standard guidelines and conduct frequent platelet counts until platelet engraftment and recovery are achieved.

There is a potential risk of neutrophil engraftment failure after treatment with lovotibeglogene autotemcel. It is recommended to monito neutrophil counts until engraftment has been achieved and provide rescue treatment with the back-up collection of CD34+ cells.

Discontinue hydroxyurea at least 2 months prior to mobilization and should not resume until ally cycles of apheresis are completed. If hydroxyurea is administered after apheresis completion, discontinue at least 2 days prior to myeloablative conditioning.

Discontinue disease modifying agents (e.g., L-glutamine, voxelotor, and crizanlizumab) at least 2 months prior to mobilization and 2 months prior to myeloablative conditioning as the interaction between the disease modifying agents and the mobilization and myeloablative conditioning agents 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 lovotibeglogene 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.

Oxbryta (voxelotor)

The HOPE trial (NCT03036813) was a multicenter, randomized, double-blind, placebo-controlled Phase 3 trial involving 274 individuals aged 12-64 years. Individuals were randomized to receive voxelotor tablets at either 1,500 mg/day, 900 mg/day, or placebo. The primary endpoint studied was the percentage of individuals who had a hemoglobin (Hb) response, defined as an increase of more than 1 g/dL from baseline to week 24. 51% of individuals in the intent-to-treat population receiving voxelotor showed a greater than 1 g/dL increase in Hb compared to baseline, versus 7% receiving placebo. 59% of individuals in the per-protocol population receiving voxelotor had a greater than 1 g/dL increase in Hb compared to baseline, compared to 10% in individuals receiving placebo. Secondary endpoints included changes in Hb level from baseline at week 24 and changes

in laboratory markers associated with hemolysis (indirect bilirubin level and percentage of reticulocytes) from baseline at week 24. 27% of individuals receiving voxelotor in the per-protocol population experienced a greater than 2 g/dL increase in Hb at week 24, compared to 1% in the placebo group. The decrease in indirect bilirubin level from baseline to week 24 was greater in the 1500mg voxelotor group than placebo.

Less than 1% of individuals treated with voxelotor experienced serious hypersensitivity reactions. A majority of adverse events were not related to sickle cell disease in the 1500mg, 900mg and placebo groups, 94%, 93% and 89% respectively. These most common adverse events, with greater than 20% incidence, were headache and diarrhea. The proportion of individuals who discontinued the study or experienced a serious adverse event did not differ across the three groups. Four individuals had fatal adverse events, three occurred in the 1500-mg group (sickle cell anemia with crisis, pulmonary sepsis and acute sickle hepatic crisis) and one sickle cell anemia with crisis in the 900-mg group. A drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in the post marketing experience with voxelotor.

References

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History

Date	Comments
02/01/24	New policy, approved January 9, 2024. For the treatment of sickle cell disease, moved Adakveo, Endari, and Oxbryta from Policy 5.01.576 to Policy 5.01.640 with no changes to coverage criteria. Added coverage for Casgevy (exagamglogene autotemcel) and Lyfgenia (lovotibeglogene autotemcel) for the treatment of sickle cell disease. Added HCPCS codes J0791 and J3590.
07/01/24	Coding update. Added new HCPCS code J3394 effective 7/1/2024. Removed drug name Lyfgenia from unlisted code, J3590.
01/01/25	Coding update. Added new HCPCS code J3392 effective 1/1/2025. Removed unlisted code J3590 for Casgevy.

and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA).

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

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呼籲提供免費的語言援助服務和適當的輔助設備及服務。
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Звертайтесь за безкоштовною мовною підтримкою та відповідними додатковими послугами.
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