Pharmacy Focus:
Casgevy™ and Lyfgenia™ — New Gene Therapies for Sickle Cell Disease

Key Takeaways

- Two new gene therapies were approved for the treatment of Sickle Cell Disease (SCD) in adults and children 12 years of age and older.
- These therapies were developed to potentially establish production of normal functioning hemoglobin to help reduce the vaso-occlusive events and complications associated with SCD.
- Costs for the one-time treatments are projected to be $2.2 million for Casgevy™ and $3.1 million for Lyfgenia™ (not including the average hospital stay of four to six weeks).

Sickle Cell Disease Overview and Approach to Managing Symptoms[1-10]

Sickle Cell Disease (SCD) is an inherited blood disorder that affects hemoglobin in red blood cells. The abnormally functioning gene that causes SCD is β-globin (HBB). This gene is responsible for making hemoglobin, which is the protein in red blood cells that is responsible for carrying oxygen. Because of the genetic abnormality, red blood cells cannot properly deliver oxygen throughout the body of a person with SCD. The name "sickle cell disease" is derived from the sickle or crescent shape of the cells created by the decreased oxygen, which leaves the cells stiff and sticky, disrupting blood flow. Obstruction to blood flow can lead to red blood cell rupture, anemia, organ damage and episodes of pain.

Sickle Cell Disease ICD-10 Codes:
D57.00-D57.2, D57.4, D57.8

There are different types of SCD, but the most common are: sickle cell anemia (HbSS), sickle cell hemoglobin-C disease (HbSC), sickle beta-zero thalassemia (HbS beta0) and sickle beta-plus thalassemia (HbS beta+). Sickle cell anemia (HbSS) is usually the most severe form of SCD, followed by sickle beta-zero thalassemia (HbS beta0). SCD affects approximately 100,000 people in the United States.

However, it is most common in those of African and Latin American descent, while also being prevalent in those of Middle Eastern, Asian and Mediterranean ancestry.

Symptoms of SCD usually appear at around five months of age. The effects of SCD can vary from person to person, and most symptoms are due to complications of the disease itself. However, early symptoms include painful swelling of the hands and feet, fatigue from anemia and jaundice, a yellowish coloring of the skin or whites of the eyes. There are various long-term complications of SCD that can range from mild to severe, including, but not limited to, infection, stroke, organ damage, pain, pulmonary hypertension and blood clots.

The goals of managing SCD include treating pain episodes and preventing other complications. Treating pain crises typically requires replenishing fluids to achieve adequate hydration and rapidly administering analgesia, specifically opioids. In addition to pain episodes, people with SCD also can experience chronic pain every day, which requires an adequate pain management plan that can include long-term opioid use. Allowing people with SCD to regularly receive scheduled opioids and other pain medications is appropriate due to the persistent pain that comes with the disease.

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Additionally, people with SCD are commonly hospitalized for extended periods. Aside from pain and vaso-occlusive episodes, they also experience infections and organ damage more often than those without SCD. All of these complications lead to more frequent emergency department visits and hospitalizations that average 13 days, though it can be longer.

To prevent episodes and additional complications, disease-modifying agents and blood transfusions are used as needed. Hydroxyurea is the first-line therapy in SCD for prevention, especially in sickle cell anemia and sickle beta-zero thalassemia, because it decreases pain episodes and other complications. Agents such as L-glutamine, Adakveo® (crizanlizumab) and Oxbryta® (voxelotor) can be added to hydroxyurea if the disease is still not controlled. A known potential cure for SCD is a bone marrow transplant; however, difficulty with finding a matched donor makes this option very rare and does not guarantee a cure for everyone. Recently, gene therapies have been showing promising results in terms of halting disease progression and potentially curing the disease. In December 2023, the gene therapies Casgevy™ and Lyfgenia™ were approved by the Food and Drug Administration (FDA).

SCD Treatment/Management Options[11-18]

Drug/ Intervention	Dosing	How It Works	Price	Adverse Events	HCPCS Code
Chronic Blood Transfusion	Variable, based on frequency of pain episodes	Provides viable red blood cells with oxygen carrying capacity	Transfusions/transfusion-related costs: **$98,000 PPY**; chelation costs **$53,000 PPY** (Total $151,000 PPY)	Allergic reactions, fever, transfusion-transmitted infections, alloimmunization, iron overload	P9010 – P9100
Allogeneic SCT/ Bone Marrow Transplant	1–3×10^8/kg of recipient weight	Provides functional HBB gene from donor	**$900,000 – $1,132,000**	Graft versus Host Disease, infections	38240
Hydroxyurea	Initial: 15 mg/kg/day Max: 35 mg/kg/day	Increases hemoglobin in red blood cells and decreases red blood cell adhesions	**$73,000 PPY** for hydroxyurea; **$5,000 PPY** for other chronic medication; emergency department visits: **average 3x/year** (**$75,000**) (Total $153,000 PPY – direct costs only)	Dry skin, myelosuppression, infection, headache	Prescription Benefits
Oxbryta® (voxelotor)	Children 4 to 12 years of age: 10kg to <20kg, 600mg daily; 20kg to <40kg, 900mg daily; >40kg, 1,500mg daily Adult dosing (12 years and up): 1,500mg daily	Inhibits red blood cell sickling, improves red blood cell deformability, and reduces whole blood viscosity	**$192,000 - $288,000 PPY** plus **$73,000 PPY** for hydroxyurea and **$5,000 PPY** for other chronic emergency department visits – average **3x/year ($75,000)** (Total $153,000 PPY – direct costs only)	Rash, diarrhea, headache, nausea, abdominal pain, hypersensitivity, pulmonary embolism	Prescription Benefits
Adakveo® (crizanlizumab)	5mg/kg every 4 weeks	Reduces interactions between red blood cells and endothelial cells	**$168,000 PPY**, plus **$73,000 PPY** for hydroxyurea and **$5,000 PPY** for other chronic medication; emergency department visits – average **3x/year ($75,000)** (Total $320,000 PPY – direct costs only)	Nausea, arthralgia, backache, fever, infusion site reaction	J0791

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Treatment/Management Options[12-22]

Drug/ Intervention	Dosing	How It Works	Price	Adverse Events	HCPCS Code
Casgevy™	3 × 106 CD34+ cells per kg of body weight, once	Gene editing therapy that reduces BCL11A expression, increasing HbF expression (functional hemoglobin)	One-time treatment estimated at **$2.2 million** plus pre-treatment and post-treatment: 4-6 weeks hospitalization (average)	Mucositis, febrile neutropenia, and decreased appetite; neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia	C9399, J3590 (temporary)
Lyfgenia™	3 × 106 CD34+ cells per kg of body weight, once	Provides addition of functional βA-globin gene via lentiviral vector leading to production of functional HbA	One-time treatment estimated at **$3.1 million** plus pre-treatment and post-treatment: 4-6 weeks hospitalization (average)	Stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia	C9399, J3590 (temporary)

**Annual price estimates based on HM Insurance Group internal reporting and additional industry knowledge, 2023.*

Therapy Spotlight: Casgevy (exagamglogene autotemcel; exa-cel)[17, 19-22]

Casgevy is a new gene therapy produced by Vertex and CRISPR Therapeutics. It was approved by the FDA December 8, 2023, under the Accelerated Approval pathway, for use in the treatment of sickle cell disease in patients 12 years and older with recurrent vaso-occlusive crises (VOCs). Casgevy is the first FDA-approved gene therapy that uses CRISPR/Cas9-editing technology for genetic modification versus the current gene therapies that utilize gene addition techniques. The estimated cost for the one-time infusion of Casgevy is $2,200,000.

Overall, the goal of Casgevy is to be a potentially curative gene therapy for sickle cell disease by providing gene editing technology to reduce BCL11A expression, the gene that is responsible for inhibiting gamma-globin and the production of functional fetal hemoglobin (HbF). HbF expression reduces intracellular hemoglobin S (HbS) concentration, preventing the red blood cells from sickling and addressing the underlying cause of disease, thereby eliminating VOCs and the increased complications and medical costs associated.

Full myeloablative conditioning must be administered between 48 hours and seven days before infusion of Casgevy. Prophylaxis for seizures should be considered prior to initiating myeloablative conditioning. The most common side effects reported were mucositis, febrile neutropenia and decreased appetite, as well as neutropenia, thrombocytopenia, leukopenia, anemia and lymphopenia. Routine follow-up lab work, monitoring, infection prophylaxis and blood cell support will be required possibly long-term.

The pinnacle CLIMB-121 trial treated 44 patients ages 12 to 35. Results showed that 93.5 percent of evaluable patients achieved the primary efficacy outcome of freedom from severe VOC episodes for at least 12 consecutive months during the 24-month follow-up period. All treated patients also achieved successful engraftment, with no patients experiencing graft failure or graft rejection. Patients who receive Casgevy will be followed in a long-term study to evaluate the product's safety and effectiveness. Casgevy also is under FDA review for another blood disease, transfusion-dependent beta thalassemia, for which the PDUFA date is March 30, 2024.

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Therapy Spotlight: Lyfgenia (lovotibeglogene autotemcel; lovo-cel)[18-19, 23-24]

Lyfgenia is a new gene therapy produced by bluebird bio. It was approved by the FDA December 8, 2023, (under the Accelerated Approval pathway) for use in the treatment of sickle cell disease in patients 12 years and older with history of vaso-occlusive crises/events (VOCs/VOEs). Lyfgenia joins Casgevy as the first FDA-approved gene therapies for sickle cell disease. Lyfgenia utilizes gene addition technology for treatment. The estimated cost for the one-time infusion of Lyfgenia is $3,100,000.

Overall, the goal of Lyfgenia is to be a potentially curative gene therapy for sickle cell disease by introducing or adding functional copies of a modified βA-globin gene into patients' hematopoietic stem cells using a lentiviral vector. The reintroduced cells combine with α-globin to produce functional Hb and red blood cell formation, which increases oxygen-binding affinity, reduces hemoglobin S (HbS) levels and inhibits polymerization of HbS (the sickling of red blood cells). This addresses the underlying cause of disease, thereby eliminating VOCs and the increased complications and medical costs associated.

Patients are required to undergo hematopoietic stem cell mobilization followed by apheresis to obtain CD34+ cells for Lyfgenia manufacturing. Myeloablative conditioning must be administered before infusion, and following myeloablative conditioning, a minimum of 48 hours of washout must be allowed before Lyfgenia infusion.

The most common side effects reported were stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia and leukopenia. Patients with α-thalassemia trait may experience anemia that may require chronic red blood cell transfusions. Routine follow-up lab work, monitoring, infection prophylaxis and blood cell support will be required possibly long-term.

The pinnacle HGB-206 study treated 32 patients ages 12-50. Results showed that 88 percent of the patients achieved the primary efficacy outcome of VOE-CR (complete resolution of vaso-occlusive events) between six and 18 months after infusion of Lyfgenia. Patients who receive Lyfgenia will be followed in a long-term study to evaluate the product's safety and effectiveness. The label will include a Boxed Warning regarding the risk for development of hematologic malignancy requiring lifelong monitoring.

Cost Containment Considerations

As part of its HMConnects™ cost containment program, HM Insurance Group (HM) works to support cost management opportunities around the use of gene and cell therapies and other high-cost pharmaceutical treatment options that can impact our clients' bottom line. The Pharmacy Operations (RxOps) team watches the market – and our book of business – to anticipate how current and future advancements will impact financial risk levels for HM's client base. Standard practices include reviewing, auditing and collaborating on the content of current policies, monitoring trends and implementing appropriate cost savings techniques. Additional practices include prevention of stockpiling, ensuring prescriptions are filled via in network pharmacies and that they are properly dosed based on weight and lab values when appropriate. All of these services are provided to HM's clients at no additional cost to them.

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Pharmacy Focus provides valuable information about pharmaceutical industry developments and their associated costs that can impact the growing claims trend in the self-funded insurance market. Be aware of influences and gain insight into approaches that may help to contain costs. Please share topic suggestions or feedback with **HMPharmacyServices@hmig.com**.

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Resources: [1]National Heart, Lung, and Blood Institute, Sickle Cell Disease, Bethesda, MD: U.S. Department of Health and Human Services, 2022, https://www.nhlbi.nih.gov/health/sickle-cell-disease, accessed November 11, 2022; [2]National Institute of Health, Fixing the Sickle Cell Disease Gene. Washington, D.C.: U.S. Department of Health and Human Services, 2021, https://www.nih.gov/news-events/nih-research-matters/fixing-sickle-cell-disease-gene, accessed November 11, 2022; [3]Centers for Disease Control and Prevention, Sickle Cell Disease (SCD), Clifton Road, Atlanta, GA: U.S. Department of Health and Human Services, 2022, https://www.cdc.gov/ncbddd/sicklecell/facts.html, accessed December 8, 2023; [4]American Society of Hematology, Sickle Cell Disease, https://www.hematology.org/education/patients/anemia/sickle-cell-disease, accessed November 11, 2022; [5]Medline Plus, Sickle Cell Disease, November 2020, https://medlineplus.gov/sicklecelldisease.html, accessed November 22, 2022; [6]Centers for Disease Control and Prevention, Sickle Cell Disease (SCD) Complications, Clifton Road, Atlanta, GA: U.S. Department of Health and Human Services, 2022, https://www.cdc.gov/ncbddd/sicklecell/complications.html, accessed November 11, 2022; [7]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; 312:1033; [8]Centers for Disease Control and Prevention, Complications of Sickle Cell Disease, https://www.cdc.gov/ncbddd/sicklecell/complications.html#Pain, accessed December 8, 2023; [9]Zakaria O M, Buhalim R A, Al Jabr F A, et al., November 06, 2021, Reasons for Hospitalization of Sickle Cell Disease Patients in the Eastern Province of Saudi Arabia: A Single-Center Study, Cureus 13(11): e19299. DOI 10.7759/cureus.19299; [10]Baldwin Z, Boshen J, Basu A, Roth J, Bender MA, et al., Medical and Non-medical Costs of Sickle Cell Disease and Treatments from a US Perspective: a Systematic Review and Landscape Analysis, Pharmecon. 2022;6:469-481; [11]Kalpatti R, Song X, Martinez D, et al. Pro35, Economic Burden of Chronic Red Blood Cell Transfusions Among Patients with Sickle Cell Disease, Elsevier. 2020;23(1):335; [12]Hydrea (hydroxyurea) Package Insert, Princeton, NJ: Bristol-Meyers Squibb, March 2016; [13]Adakveo (crizanlizumab) Package Insert, East Hanover, NJ: Novartis, November 2019; [14]Centers for Disease Control and Prevention, Sickle Cell Data Collection (SCDC) Program, https://www.cdc.gov/ncbddd/hemoglobinopathies/scdc-voe-data-brief.html, accessed November 21, 2022; [15]Shah N, Bhor M, Xie L, Halloway R, Arcona S, et al., Treatment Patterns and Economic Burden of Sickle Cell Disease Patients Prescribed Hydroxyurea: A Retrospective Claims-Based Study; [16]Oxbryta (voxelotor) Package Insert. San Francisco, CA, November 2019; [17]Casgevy (exagamglogene autotemcel, exa-cel) Package Insert, Boston, MA, December 2023; [18]Lyfgenia (Lovotibeglogene autotemcel (AKA lovo-cel) Package Insert, Somerville, MA, December 2023; [19]Emerging Therapy Solutions® (ETS) Announcement, December 2023 – Two New Sickle Cell Disease Gene Therapies Approved Today, Accessed December 8, 2023; [20]CRISPR Therapy for Sickle Cell Approved by FDA in Gene Editing Milestone https://www.biopharmadive.com/news/crispr-fda-approval-sickle-cell-gene-editing-vertex-casgevy/701522/, accessed December 08, 2023; [21]Vertex and CRISPR Therapeutics Announce US FDA Approval of Casgevy™ (exagamglogene autotemcel) for the Treatment of Sickle Cell Disease, https://news.vrtx.com/news-releases/news-release-details/vertex-and-crispr-therapeutics-announce-us-fda-approval, accessed December 08, 2023; [22]A Safety and Efficacy Study Evaluating CTX001 in Subjects With Severe Sickle Cell Disease, https://clinicaltrials.gov/study/NCT03745287?term=NCT03745287&rank=1, accessed December 08, 2023; [23]bluebird bio Announces FDA Approval of Lyfgenia™ (lovotibeglogene autotemcel) for Patients Ages 12 and Older with Sickle Cell Disease and a History of Vaso-Occlusive Events, https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-announces-fda-approval-lyfgeniatm-lovotibeglogene, accessed December 8, 2023; [24]A Study Evaluating the Safety and Efficacy of bb1111 in Severe Sickle Cell Disease, https://clinicaltrials.gov/study/NCT02140554?term=NCT02140554&rank=1, accessed December 8, 2023.

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