Pharmacy Focus:
LentiGlobin – A New Gene Therapy for Sickle Cell Disease

Key Takeaways Regarding LentiGlobin

- In the pipeline to be approved for the treatment of sickle cell disease in adults and children 2 years of age and older
- Offers a one-time therapy to potentially establish production of normal functioning hemoglobin to help reduce vaso-occlusive events and complications of SCD
- Market price expected around $2,800,000 for a one-time dose, not including the average hospital stay of 44 days

Sickle Cell Disease Overview and Current Treatment[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 delivery 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 to be stiff and sticky, disrupting blood flow. Obstruction to blood flow can lead to red blood cell rupture, anemia, organ damage, and pain episodes.

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 beta^0), 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 beta^0). 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 descent.

Variants of Sickle Cell Disease:

Inherited Variants	Type of Sickle Cell Disease (* = qualifies for LentiGlobin for SCD)
HbS + HbS	Sickle cell anemia*
HbS + Hb β0-thalassemia	Sickle beta-zero thalassemia*
HbS + Hb β+-thalassemia	Sickle beta-plus thalassemia*
HbS + HbC	Sickle cell hemoglobin-C disease
HbS + (HbD, HbE, HbO)	Sickle cell hemoglobin D, E, or O disease
ICD Codes: D57.00-03, D57.438-44, D57.09-219, D57.451-452, D57.40, D57.458-459, D57.411-413, D57.80-813, D57.418-42, D57.81	

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Symptoms of SCD usually appears 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 hands and feet, fatigue from anemia, and jaundice, which causes a yellowish color 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.

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 longer hospitalizations with an average length of stay at 13 days, though it can be longer.

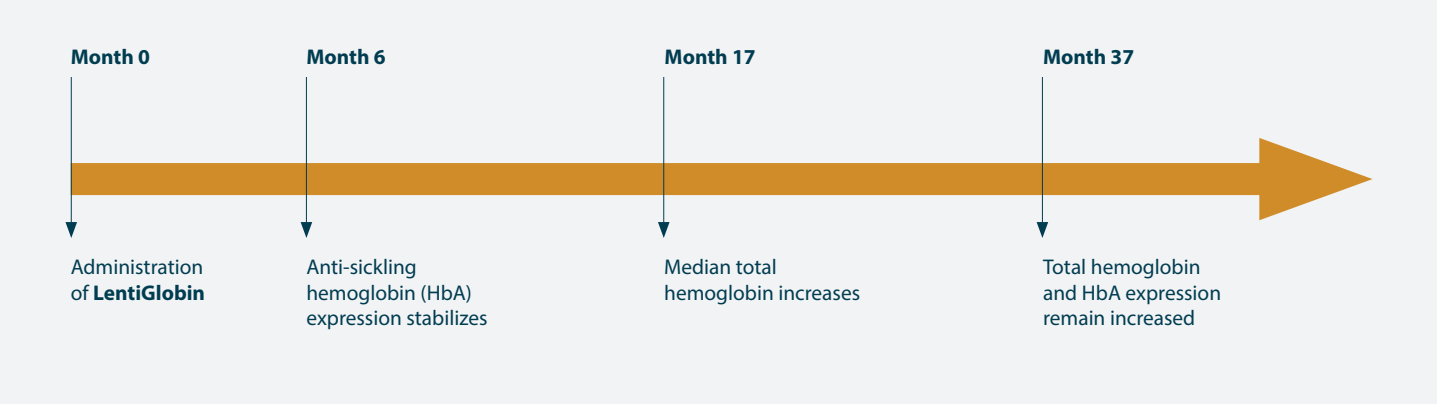
To prevent these episodes and further complications, disease-modifying agents and blood transfusions are used as needed. Hydroxyurea is the first-line therapy in SCD for prevention, especially in sickle cell anemia and sickle beta-zero thalassemia, because it decreases pain episodes and other complications. Agents such as L-glutamine and Adakveo® (crizanlizumab) 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 finding a matched donor makes this option very rare and does not guarantee a cure for everyone. Recently, gene therapies, such as one promoted by the name LentiGlobin, have been showing promising results of halting disease progression and potentially curing the disease.

LentiGlobin Overview[11]

LentiGlobin is a new gene therapy produced by bluebird bio for sickle cell disease. It is not yet FDA approved but is projected to be launched in 2023. bluebird bio has stated that they are on track to file its biologics licensing application (BLA) in the first quarter of 2023. The price of LentiGlobin is anticipated to be around $2,800,000. LentiGlobin also will require a hospital stay of 44 days for neutrophil engraftment after infusion. Some common post-infusion side effects reported include abdominal pain, drug withdrawal syndrome, nausea and vomiting.

Treatment with LentiGlobin will allow the body to produce anti-sickling hemoglobin (HbA) to eliminate vaso-occlusive episodes and other complications of SCD. According to bluebird bio's phase I/II trial of LentiGlobin, adequate expression of HbA is expected to develop six months post treatment. Participants in this study were followed for 37 months and maintained an increased hemoglobin level with no incidences of vaso-occlusive episodes.

LentiGlobin Treatment Timeline:



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Treatment/Management Options[12-22]

	Hydroxyurea	Adakveo® (crizanlizumab)	Chronic Blood Transfusion	Bone Marrow Transplant	LentiGlobin
Indication	Sickle cell disease	Sickle cell disease	Sickle cell disease	Sickle cell disease	Sickle cell disease
Method	Increases hemoglobin in RBCs and decreases RBC adhesions	Reduces interactions between RBCs and endothelial cells	Provides viable RBCs with oxygen-carrying capacity	Provides functional HBB gene from donor	Inserts functional HBB gene via lentiviral vector
Annual Price*	**Treatment:** $73,000 PPY for hydroxyurea; $5,000 PPY for other chronic medication **ED visits:** 3x/year (average) $75,000 **Total:** $153,000 PPY (direct costs only)	**Treatment:** $168,000 PPY, plus $73,000 PPY for hydroxyurea; $5,000 PPY for other chronic medication **ED visits:** 3x/year (average) $75,000 **Total:** $320,000 PPY (direct costs only)	**Treatment:** Transfusions/ transfusion-related: $98,000 PPY **Chelation costs:** $53,000 PPY **Total:** $151,000 PPY	**Treatment:** One-time transplant: $150,000 (median price)	**Pre-treatment:** Busulfan, G-CSF, Plerixafor **One-time treatment:** estimated at $2.8 million **Post-treatment:** 44-day hospitalization (average); possible chronic G-CSF use
Dosing	**Initial:** 15 mg/kg/day **Max:** 35 mg/kg/day	5mg/kg every 4 weeks	Variable, based on frequency of pain episode	N/A	5.0 × 106 CD34+ cells/kg
Adverse Events	Dry skin, myelosuppression, infection, headache	Nausea, arthralgia, backache, fever, infusion site reaction	Fever, allergic reactions, transfusion-transmitted infections, alloimmunization, iron overload	Graft versus Host Disease, infections	Abdominal pain, drug withdrawal syndrome, nausea, vomiting

**Annual price estimates based on HM Insurance Group internal reporting and additional industry knowledge, 2022.*

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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 identifying the stockpiling of medications, determining if prescriptions are filled via in-network pharmacies and confirming that prescriptions 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.

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]Sickle Cell Disease, National Heart, Lung, and Blood Institute, 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]Fixing the Sickle Cell Disease Gene, National Institute of Health, 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]Sickle Cell Disease (SCD) Centers for Disease Control and Prevention, Clifton Road Atlanta, GA: U.S. Department of Health and Human Services, 2022, https://www.cdc.gov/ncbddd/sicklecell/facts.html, accessed November 11, 2022; [4]Sickle Cell Disease, American Society of Hematology, https://www.hematology.org/education/patients/anemia/sickle-cell-disease, accessed November 11, 2022; [5]Sickle Cell Disease, Medline Plus, November 2020, https://medlineplus.gov/sicklecelldisease.html, accessed November 11, 2022; [6]CSickle Cell Disease (SCD) Complications, Centers for Disease Control and Prevention, 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; 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