Pharmacy Focus:
Gene Therapies for Beta Thalassemia — Zynteglo® and Casgevy™

Key Takeaways

- Two gene therapies are approved for the treatment of transfusion-dependent beta thalassemia (TDT) in adults and children: Zynteglo® (August 2022) and Casgevy™ (January 2024).
- The therapies were designed to potentially establish production of normal functioning hemoglobin to help reduce associated anemia and transfusion dependence.
- The estimated costs of the one-time treatments are $2.8 million for Zynteglo® and $2.2 million for Casgevy™. (Costs do not include the average hospital stay of four to six weeks.)

Beta Thalassemia Disease Overview[1-7]

Beta Thalassemia is a genetic blood disorder that results in a reduction in the function of hemoglobin, which is the blood component in charge of oxygen transport. The gene responsible for this disorder is hemoglobin subunit beta (HBB). This gene also is associated with other forms of anemias and sickle cell disease (shared for reference but not covered in this document).

About 1,300 individuals in the United States are estimated to have beta thalassemia, which has different severities – thalassemia minor, thalassemia intermedia and thalassemia major (also known as Cooley's Anemia). The severity of the disorder depends on the number of affected genes a person has inherited and determines the level of treatment required (see "Beta Thalassemia Severities" table).

Beta thalassemia is most common in people of Mediterranean, North African, Indian, Central Asian and Southeast Asian descent. There is an equal risk between males and females for inheriting the disease since it is an autosomal recessive disease. Forty-four states and all U.S. territories require newborn testing for beta thalassemia, which is completed with a heel stick and blood panel.

Symptoms of beta thalassemia can become evident anywhere from one month through 11 years of age. The hallmark presentation of this disorder is anemia, due to abnormal hemoglobin, which can be life-threatening in severe cases. As the individual ages, they may have slowed growth, pallor, jaundice, gallstones and liver inflammation/enlargement. Other severe symptoms include failure to thrive and bone abnormalities. If a patient with thalassemia major does not receive treatment, they usually do not survive past the first few years of life due to cardiac complications. For females of childbearing age with beta thalassemia, fertility can be impacted, and pregnancies can be high-risk with complications.

Beta Thalassemia Severities[2,8,9]

Carrier/Minor	Intermediate/Intermedia	Major/Cooley's Anemia
• Asymptomatic • Mild anemias • No treatments required • One affected gene	• Mild/moderate anemias within early childhood to later in life • Slowed growth • Bone abnormalities • Two affected genes	• Life-threatening anemias within the first two years • **Transfusion-dependent** • Slowed growth • Bone abnormalities • Spleen/liver enlargement • Two affected genes • Rare: One dominant affected gene
ICD Code: D56.3	**ICD Code: D56.1**	**ICD Codes: D56.1, D56.5**

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Current Treatment Options[5,10,11,12]

As of early 2022, there were very few therapies to correct disease progression. Rather, the standard of care has consisted of management strategies that are time-consuming with the potential for adverse consequences requiring additional treatment. Current standard therapy requires lifelong blood transfusions and iron removal treatment for symptomatic individuals.

Thalassemia major patients can be described as transfusion-dependent, as these individuals receive blood transfusions every three to four weeks indefinitely. Chronic blood transfusions can lead to life-threatening iron overload complications that result in heart, liver and, possibly, hormonal problems. Iron overload is corrected with chelation drugs, such as Desferal® (Deferoxamine) and Exjade®/ Jadenu®(Deferasirox), that remove excess iron from the blood.

Reblozyl® is another option for managing anemia related to beta thalassemia major where blood cell maturation is increased via injections every three weeks. The only potential cure for beta thalassemia is a sibling matched bone marrow transplant; however, transplant matches are extremely rare and infrequent due to genetic match incompatibilities.

Therapy Spotlight: Zynteglo® (betibeglogene autotemcel)[13-18]

Zynteglo® is a gene therapy for beta thalassemia produced by bluebirdbio. Zynteglo® was FDA-approved August 17, 2022, for use in pediatric (four years of age and older) and adult patients who are transfusion-dependent. The manufacturer set the price for the one-time treatment at $2,800,000.

Patients receiving Zynteglo® can expect about 15 days of pretreatments consisting of myeloablative/chemotherapy and mobilization therapy to help the body prepare for the treatment. Then, the average hospitalization duration post-treatment is about 44 days. Some patients found it necessary to continue the use of their mobilization therapies (G-CSF) after treatment indefinitely. Some reported side effects that include mucositis, fever, vomiting and pain.

Overall, the goal is for patients to become transfusion-independent due to a one-time Zynteglo® treatment. According to bluebirdbio's Phase I/II combined studies, their initial participants are taking two months to reach transfusion independence and experience 17 months of transfusion independence after the one-time treatment. Phase III data used a higher FDA-approved dose and found a median duration of transfusion independence to be 31.6 months.

Therapy Spotlight: Casgevy™ (exagamglogene autotemcel; exa-cel)[21-25]

Casgevy™ is a new gene therapy produced by Vertex and CRISPR Therapeutics. It was approved by the FDA two months early on January 16, 2024, under the Accelerated Approval pathway for use in the treatment of transfusion-dependent beta thalassemia (TDT) in patients 12 years and older. 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. Casgevy™ was previously approved December 8, 2023, for the treatment of severe sickle cell anemia. The estimated cost for the one-time infusion of Casgevy™ is $2,200,000.

Overall, the goal of Casgevy™ is to ameliorate anemia and achieve transfusion independence with the one-time treatment. Casgevy™ provides gene-editing technology to reduce BCL11A expression, the gene that is responsible for inhibiting gamma globin and the production of functional fetal hemoglobin (HbF). To help the body prepare for the treatment, pretreatments, which consist of myeloablative/chemotherapy and mobilization therapy, should be expected for up to 15 days prior to administration 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 may be required – possibly long-term.

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The pinnacle CLIMB-111 trial treated 35 patients ages 12 to 35. Results showed that 91.4 percent of evaluable patients achieved the primary end point/efficacy outcome of achieving transfusion independence for at least 12 consecutive months – from 60 days after the last RBC transfusion up to 24 months post-Casgevy™ infusion. Patients who receive Casgevy™ will be followed in a long-term study to evaluate the product's safety and effectiveness.

Treatment Options[5,9,10,13,15,17-20, 21-25]

	Chronic Blood Transfusion	Zynteglo®	Casgevy™	Reblozyl®	Bone Marrow Transplant
Indication	Transfusion-dependent Thalassemia (ICD-10 Codes: D56.1, D56.5)	Transfusion-dependent Thalassemia (ICD-10 Codes: D56.1, D56.5)	Transfusion-dependent Thalassemia (ICD-10 Codes: D56.1, D56.5)	Transfusion-dependent Thalassemia (ICD-10 Codes: D56.1, D56.5)	Transfusion-dependent Thalassemia (ICD-10 Codes: D56.1, D56.5)
HCPCS Codes (temporary)	P9010	*J3490, J3590, C9399	*J3490, J3590, C9399	J0896	S2150
Method	Provides viable red blood cells with oxygen-carrying capacity	Inserts functional HBB gene via lentiviral vector	Gene-editing therapy that reduces BCL11A expression, increasing HbF expression (functional hemoglobin)	Matures functional red blood cells	Provides functional HBB gene from donor
Annual Price*	**Transfusions:** $22,478 PPY average **Chelation:** $52,718 PPY average **Average overall cost (2019):** $128,060	**Pre-treatment:** Busulfan, G-CSF, Plerixafor **One-time treatment:** $2.8 million **Post-treatment:** 44-day hospitalization (average); possible chronic G-CSF use	**Pre-treatment:** Busulfan, G-CSF, Plerixafor **One-time treatment:** estimated at $2.2 million **Post-treatment:** 4 to 6 weeks hospitalization (average)	<$250,000 PPY	**One-time transplant:** $150,000 median price; may still require chelation therapy
Dosing	Transfusions every three to four weeks; chelation therapy as needed according to iron levels	5.0×10^6 CD34+ cells/kg	3×10^6 CD34+ cells/kg	1-1.75 mg/kg every three weeks	N/A
Adverse Events	Fever, allergic reactions, transfusion-transmitted infections, alloimmunization, iron overload	Mucositis, febrile neutropenia, vomiting, fever, alopecia, pain, cough, headache	Mucositis, febrile neutropenia and decreased appetite; neutropenia, thrombocytopenia, leukopenia, anemia, lymphopenia	Thrombosis, high blood pressure, blood cells accumulating in the spleen	Graft vs. Host disease, infections

**Blood transfusions are billed under medical coverage, while chelation therapy is billed under prescription coverage.*

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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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