Pharmacy Focus:
Zynteglo® – New Gene Therapy for Beta Thalassemia

Beta Thalassemia Disease Overview[1,2,3,4,5,6,7]

Beta Thalassemia is a genetic blood disorder resulting in a reduction in function of the 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 (for reference but uncovered 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 table below).

Beta thalassemia is most common among 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**

Continued...

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.

Thalassemia major patients can be described as transfusion-dependent. These individuals receive blood transfusions every three to four weeks indefinitely. Chronic blood transfusions can lead to life-threatening iron overload complications resulting in heart, liver and, possibly, hormonal problems. These are corrected with chelation drugs that remove excess iron from the blood. Some common iron-removing agents include Desferal® (Deferoxamine) and Exjade®/Jadenu® (Deferasirox). These are used as needed to prevent iron toxicity.

Current standard therapy requires lifelong blood transfusions and iron removal treatment for symptomatic individuals. Reblozyl® is another option for managing anemia related to beta thalassemia major where blood cell maturation is increased via injections every three weeks. It is expected to decrease the number of necessary blood transfusions. 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.

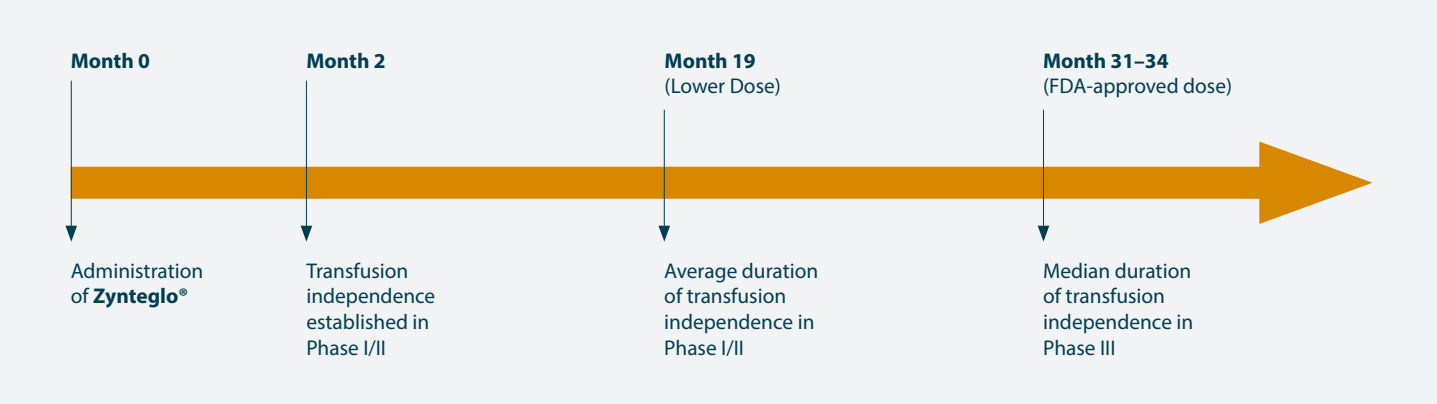
Zynteglo® Overview [13,14,15,16,17,18]

Zynteglo® is a new gene therapy for beta thalassemia produced by bluebird bio. Zynteglo® was FDA-approved on August 17, 2022, for use in pediatric 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 have found it necessary to continue the use of their mobilization therapies (G-CSF) after treatment indefinitely. Some also reported side effects including mucositis, fever, vomiting and pain.

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

Zynteglo® Treatment Timeline[16,17]



Continued...

Treatment Options[5,9,10,13,15,17,18,19,20]

	Chronic Blood Transfusion	Zynteglo®	Reblozyl®	Bone Marrow Transplant
Indication	Transfusion-dependent Thalassemia (ICD-10 Code: D56.1, D56.5)	Transfusion-dependent Thalassemia (ICD-10 Code: D56.1, D56.5)	Transfusion-dependent Thalassemia (ICD-10 Code: D56.1, D56.5)	Transfusion-dependent Thalassemia (ICD-10 Code: D56.1, D56.5)
HCPCS Codes (temporary)	P9010	J3490, J3590, C9399	J0896	S2150
Method	Provides viable red blood cells with oxygen-carrying capacity	Inserts functional HBB gene via lentiviral vector	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	<$250,000 PPY	**One-time transplant:** $150,000 median price; may still require chelation therapy
Dosing	Transfusions every 3-4 weeks; chelation therapy as needed according to iron levels	5.0 × 106 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	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*

Continued...

Key Takeaways Regarding Zynteglo®

- Gene therapy approved August 17, 2022, for adult and pediatric transfusion-dependent beta thalassemia patients
- Offers a one-time therapy to potentially establish transfusion independence
- Market price of $2,800,000 for the one-time dose without including the average hospital stay of 44 days

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.

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**.

HM Insurance Group

800.328.5433 | hmig.com

Resources: [1]Beta-thalassemia | Genetic and Rare Diseases Information Center (GARD) – an NCATS Program, Nih.gov., published 2018, https://rarediseases.info.nih.gov/diseases/871/beta-thalassemia, accessed August 5, 2022; [2]Beta Thalassemia: MedlinePlus Genetics, medlineplus.gov, published 2015, https://medlineplus.gov/genetics/condition/beta-thalassemia/#frequency, accessed August 5, 2022; [3]MedlinePlus HBB Gene: MedlinePlus Genetics, medlineplus.gov, published August 18, 2020, https://medlineplus.gov/genetics/gene/hbb/#conditions, accessed August 15, 2022; [4]Newborn Screening in Your State | Newborn Screening, newbornscreening.hrsa.gov, published June 2022, https://newbornscreening.hrsa.gov/your-state, accessed August 10, 2022; [5]Cappellini M. Éditorial. Alsic. 2019, 4 (Vol. 22, n° 2):23, 212-214. doi:10.4000/alsic.4159; [6]Beta Thalassemia, www.hopkinsmedicine.org, published July 2, 2020, https://www.hopkinsmedicine.org/health/conditions-and-diseases/beta-thalassemia?adlt=strict, accessed August 8, 2022; [7]NORD-estimate Beta Thalassemia, NORD (National Organization for Rare Disorders), rarediseases.org, accessed August 2022; [8]ICD-10-CM Code D56.3 – Beta thalassemia minor, ICD Codes, published 2022, https://icd.codes/icd10cm/D563, accessed August 15, 2022; [9]ICD-10-CM Code D56.1 - Beta thalassemia, ICD Codes, published 2022, https://icd.codes/icd10cm/D561, accessed August 5, 2022; [10]Thalassemia - Treatment | NHLBI, NIH. www.nhlbi.nih.gov, published June 1, 2022, https://www.nhlbi.nih.gov/health/thalassemia/treatment, accessed August 5, 2022; [11]Iron Chelation Therapy | Boston Children's Hospital, https://www.childrenshospital.org/treatments/iron-chelation-therapy, accessed August 18, 2022; [12]Bristol Myers Squibb, Highlights of Prescribing Information, 2022, https://packageinserts.bms.com/pi/pi_reblozyl.pdf, accessed August 19, 2022; [13]bluebird Provides Update on FDA Review Timelines for Betibeglogene Autotemcel (beti-cel) for Beta-Thalassemia and Elivaldogene Autotemcel (eli-cel) for Cerebral Adrenoleukodystrophy (CALD) | bluebird bio, Inc., published 2022, https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-provides-update-fda-review-timelines-betibeglogene?adlt=strict, accessed August 10, 2022; [14]bluebird bio Announces Launch in Germany of ZYNTEGLO™ (autologous CD34+ cells encoding βA-T87Q-globin gene) Gene Therapy for Patients 12 Years and Older with Transfusion-Dependent β-Thalassemia Who Do Not Have $\beta^0/\beta 0$ Genotype - bluebird bio, Inc., investor.bluebirdbio.com, published 2020, https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-announces-launch-germany-zynteglotm-autologous-cd34, accessed August 10, 2022; [15]Highlights of Prescribing Information, 2022, https://www.bluebirdbio.com/-/media/bluebirdbio/CorporateCOM/Files/Zynteglo/ZYNTEGLO_prescribing_information.pdf, accessed August 18, 2022; [16]bluebird bio, A Phase 1/2 Open Label Study Evaluating the Safety and Efficacy of Gene Therapy in Subjects With β-Thalassemia Major by Transplantation of Autologous CD34+ Cells Transduced Ex Vivo With a Lentiviral βA-T87Q-Globin Vector (LentiGlobin® BB305 Drug Product), clinicaltrials.gov, published April 16, 2019, https://clinicaltrials.gov/ct2/show/NCT01745120, accessed August 10, 2022; [17]Beaudoin F, Richardson M, Synnott P, Betibeglogene Autotemcel for Beta Thalassemia: Effectiveness and Value Final Evidence Report Prepared For.; 2022:D19, https://icer.org/wp-content/uploads/2021/11/ICER_Beta-Thalassemia_Final-Report_071922.pdf, accessed August 18, 2022; [18]bluebird bio Announces U.S. Commercial Infrastructure to Enable Patient Access to ZYNTEGLO®, the First and Only FDA-Approved Gene Therapy for People with Beta-Thalassemia Who Require Regular Red Blood Cell Transfusions | bluebird bio, Inc., published August 17, 2022, https://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-announces-us-commercial-infrastructure-enable, accessed August 18, 2022; [19]Paramore C, Vlahiotis A, Moynihan M, Cappell K, Ramirez-Santiago A, Treatment Patterns and Costs of Transfusion and Chelation in Commercially-Insured and Medicaid Patients with Transfusion-Dependent β-Thalassemia, Blood, 2019;130 (Supplement 1):5635-5635, doi:10.1182/blood.V130.Suppl_1.5635.5635; [20]Weiss M, Parisi Jun M, Sheth S, Clinical and economic burden of regularly transfused adult patients with β-thalassemia in the United States: A retrospective cohort study using payer claims, American Journal of Hematology. 2019;94(5). doi:10.1002/ajh.25429

MTG-3447 (8/22)