



MASSACHUSETTS

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## Medical Policy

### Gene Therapies for Thalassemia

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#### Policy Number: 215

BCBSA Reference Number: 5.01.42 (For Plan internal use only)

NCD/LCD: N/A

#### Related Policies

Prior Authorization Request Form for Zynteglo® (Betibeglogene autotemcel), #[216](#)

#### Policy

#### Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue<sup>SM</sup> and Medicare PPO Blue<sup>SM</sup> Members

Zynteglo® (Betibeglogene autotemcel) is considered **MEDICALLY NECESSARY** and may be covered for individuals with transfusion-dependent  $\beta$ -thalassemia if the following criteria are met:

1. Documented diagnosis of  $\beta$ -thalassemia by globin gene testing; **AND**
2. Require regular peripheral blood transfusions to maintain target hemoglobin levels; **AND**
3. Documented history of receiving transfusions of  $\geq 100$  ml per kilogram of body weight of packed red cells per year or who had disease that had been managed under standard thalassemia guidelines with  $\geq 8$  transfusions per year in the previous 2 years at the time of treatment decision; **AND**
4. Karnofsky performance status of  $\geq 80$  for adults ( $\geq 16$  years of age) or a Lansky performance status of  $\geq 80$  for adolescents ( $< 16$  years of age); **AND**
5. Negative serologic test for HIV infection (as per US FDA prescribing label, apheresis material from individuals with a positive test for HIV will not be accepted for Betibeglogene autotemcel manufacturing); **AND**
6. Individual does not have
  - i. A provider-determined unacceptable risk-benefit with a willing and available human leukocyte antigen-identical or human leukocyte antigen-matched donor; **OR**

- ii. T2\*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec or other evidence of severe iron overload in the opinion of treating physician; **OR**
- iii. Advanced liver disease (meets any one of the following):
  - a. Persistent aspartate transaminase, alanine transaminase, or direct bilirubin value greater than 3 times the upper limit of normal; **OR**
  - b. Baseline prothrombin time or partial thromboplastin time greater than 1.5 times the upper limit of normal; **OR**
  - c. Magnetic resonance imaging of the liver demonstrating clear evidence of cirrhosis; **OR**
  - d. Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis; **OR**
- iv. Baseline estimated glomerular filtration rate less than 70 mL/min/1.73 m<sup>2</sup>; **OR**
- v. History of receiving prior gene therapy or allogenic hematopoietic stem cell transplant; **OR**
- vi. Any prior or current malignancy (with the exception of adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin) or myeloproliferative or significant immunodeficiency disorder; **OR**
- vii. Any immediate family member (i.e. parent or siblings) with a known Familial Cancer Syndrome (including but not limited to hereditary breast and ovarian cancer syndrome, hereditary nonpolyposis colorectal cancer syndrome and familial adenomatous polyposis); **OR**
- viii. Active, uncontrolled HCV or HBV infection; **OR**
- ix. Contraindication to the use of granulocyte colony stimulating factor (G-CSF), plerixafor, busulfan, or any other medicinal products required during myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients; **OR**
- x. A white blood cell count less than 3 X 10<sup>9</sup>/L, and/or platelet count less than 100 X 10<sup>9</sup>/L not related to hypersplenism.

**NOTE:** To support the data requirements for an outcomes-based agreement on this drug, the prescriber is encouraged to provide ongoing clinical information upon request by Plan or Plan's authorized representative (Evio Pharmacy Solutions).

Betibeglogene autotemcel is considered **INVESTIGATIONAL** when the above criteria are not met.

Repeat treatment of betibeglogene autotemcel is considered **INVESTIGATIONAL**.

Betibeglogene autotemcel is considered **INVESTIGATIONAL** for all other indications.

## **Policy Guidelines**

**Recommended Dose:** The minimum recommended dose is 5.0 X 10<sup>6</sup> CD34+ cells/kg of body weight.

**Dosing Limits:** 1 injection per lifetime

**Other considerations**

- Prophylaxis for hepatic veno-occlusive disease is recommended. Prophylaxis for seizures should be considered.
- Monitor platelet counts until platelet engraftment and recovery are achieved. Individuals should be monitored for thrombocytopenia and bleeding.
- Monitor absolute neutrophil counts after betibeglogene autotemcel infusion. If neutrophil engraftment does not occur administer rescue cells.
- Monitor individuals at least annually for hematologic malignancies for at least 15 years after betibeglogene autotemcel infusion.
- Individuals should not take prophylactic anti-retroviral medications or hydroxyurea for at least 1 month prior to mobilization or the expected duration for elimination of the medications, and until all cycles of apheresis are completed as anti-retroviral medications may interfere with manufacturing of the apheresed cells.
- Iron chelators should be discontinued at least 7 days prior to initiation of conditioning. After betibeglogene autotemcel infusion, avoid use of these iron chelators for 6 months. If iron chelation is needed, consider administration of non-myelosuppressive iron chelators. Phlebotomy can be used in lieu of iron chelation, when appropriate.

## Prior Authorization Information

### Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

### Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is <b>required*</b>
Commercial PPO and Indemnity	Prior authorization is <b>required*</b>
Medicare HMO Blue <sup>SM</sup>	Prior authorization is <b>required*</b>
Medicare PPO Blue <sup>SM</sup>	Prior authorization is <b>required*</b>

Prior Authorization Request Form: Zynteglo™ (Betibeglogene autotemcel) for Beta thalassemia

\*This form must be completed and faxed to: Medical and Surgical: 1-888-282-0780; Medicare Advantage: 1-800-447-2994.

Prior Authorization Request Form for Zynteglo® (Betibeglogene autotemcel), [#216](#)

## CPT Codes / HCPCS Codes / ICD Codes

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.*

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

**The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

## HCPCS Codes

HCPCS codes:	Code Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

## ICD-10 Procedure Codes

ICD-10 PCS Procedure Codes	Code Description
XW133B8	Transfusion of Betibeglogene Autotemcel into Peripheral Vein, Percutaneous Approach, New Technology Group 8
XW143B8	Transfusion of Betibeglogene Autotemcel into Central Vein, Percutaneous Approach, New Technology Group 8

## Summary

### $\beta$ -Thalassemia

It is an inherited blood disorder that occurs as a result of a genetic variant in the HBB gene that codes for the production of  $\beta$ -globin chains. As a result, there is reduced synthesis or absence of  $\beta$ -globin chains leading to impaired production of hemoglobin. The clinical presentation is that of anemia which requires iron supplementation and multiple downstream sequelae from the disease. These sequelae include growth retardation, skeletal changes (particularly in the face and long bones of the legs), osteoporosis, leg ulcers, and development of extramedullary masses. High output heart failure from anemia is also common without treatment. Without transfusion therapy, such patients die within the first few years of life, primarily from heart failure or infection.

Life expectancy of individuals with transfusion-dependent  $\beta$ -thalassemia is much lower than population norms. From 2011 to 2021 the median age of death for a person in the US with transfusion-dependent  $\beta$ -thalassemia was 37.2. Additionally, individuals with transfusion-dependent  $\beta$ -thalassemia report decreased quality of life due to the impact on physical and mental health.

All humans have 2 copies of the HBB gene, and each copy produces the  $\beta$ -globin protein. Different types of  $\beta$ -thalassemia categorized by genotype are summarized in Table 1. When only 1 HBB gene is affected, the phenotype is less severe, and individuals are generally asymptomatic due to compensation from the other normal gene. These individuals are called  $\beta$ -thalassemia minor or carrier. However, if both copies of HBB gene are affected there is a quantitative reduction or absence of  $\beta$ -globin protein. Phenotypes that manifest as a reduction in  $\beta$ -globin chains are referred to as " $\beta$ -thalassemia intermedia" and phenotypes that manifest as absence in  $\beta$ -globin chains are called " $\beta$ -thalassemia major".

More recently, patients have been classified according to their transfusion status (i.e., transfusion-dependent  $\beta$ -thalassemia or non-transfusion-dependent  $\beta$ -thalassemia). For this evidence review, we will focus on transfusion-dependent  $\beta$ -thalassemia patients which generally includes " $\beta$ -thalassemia major" but occasionally may include patients with " $\beta$ -thalassemia intermedia". Clinical studies reviewed define "transfusion dependence" as history of at least 100 mL/kg/year of peripheral red blood cells or  $\geq 8$  transfusions of peripheral red blood cells per year for the prior 2 years. "Transfusion independence" was defined as a weighted average hemoglobin (Hb) of at least 9 g/dL without any transfusions for a continuous period of at least 12 months at any time during the study after infusion of betibeglogene autotemcel.

**Table 1. Different Types of  $\beta$ -Thalassemia<sup>5,6,7</sup>.**

Type	Genotype	Description
$\beta$ -thalassemia major (generally transfusion dependent)	$\beta^0/\beta^0$ or $\beta^0/\beta^+$	<ul style="list-style-type: none"> <li>Presents within the first 2 years of life with severe microcytic anemia (typical hemoglobin 3 to 4 g/dL), mild jaundice, and hepatosplenomegaly</li> </ul>

		<ul style="list-style-type: none"> <li>Requires regular red blood cell transfusions and other medical treatments</li> </ul>
Thalassemia intermedia	$\beta^+/\beta^+$	<ul style="list-style-type: none"> <li>Presents at a later age with similar, but milder, clinical signs and symptoms of thalassemia</li> <li>Moderately severe anemia; some may need regular blood transfusion</li> </ul>
Thalassemia minor	$\beta/\beta^0$ or $\beta/\beta^+$	<ul style="list-style-type: none"> <li>Also called “<math>\beta</math>-thalassemia carrier” or “<math>\beta</math>-thalassemia trait”</li> <li>Usually clinically asymptomatic but may have a mild anemia</li> <li>Generally do not require any treatment</li> </ul>

$\beta^0$  refers to no beta globin production;  $\beta^+$  refers to decreased beta globin production

**Epidemiology**

$\beta$ -thalassemia is one of the most common monogenic disorders, but its incidence varies geographically. Higher incidence and prevalence have been reported among individuals from Mediterranean, Africa, the Middle East, and Southeast Asia. While its occurrence is rare in United States, the pattern shows an increasing trend with migration and is expected to increase in the future. According to Bluebird Bio, approximately 1500 people in the United States currently live with transfusion-dependent  $\beta$ -thalassemia.<sup>8</sup>

**Diagnosis**

The diagnostic pathway for symptomatic thalassemia syndromes (thalassemia major and thalassemia intermedia) in a neonate, infant, or child begins with either recognition of symptoms (anemia, evidence of hemolysis and extramedullary hematopoiesis such as jaundice, skeletal abnormalities, and/or splenomegaly) or may be suspected based on a known family history. Initial laboratory testing includes a complete blood count, review of the blood smear, and iron studies. DNA-based genotyping of globin gene can be done relatively inexpensively, is required for precise diagnosis, and is especially important in carrier detection, prenatal testing, and genetic counseling.<sup>5</sup>

**Treatment**

The current standard of care for transfusion-dependent  $\beta$ -thalassemia includes blood transfusion, iron chelation therapies, and allogenic hematopoietic stem cell transplant.

As per the 2014 Thalassemia International Federation guidelines, transfusion is indicated when hemoglobin levels are less than 7 g/dL on 2 different occasions more than 2 weeks apart, or when hemoglobin levels are greater than 7 g/dL but there are co-occurring complications such as facial changes, poor growth, fractures, or clinically significant extramedullary hematopoiesis. The goal of treatment is to maintain a hemoglobin level of 9 to 10.5 g/dL, which has been shown to promote normal growth, suppress bone marrow activity, and minimize iron accumulation.<sup>9,10</sup> Transfusions are typically required every 2 to 5 weeks to reach this goal but can vary for patients such as those with heart failure who may require higher target hemoglobin levels.<sup>11</sup> Risks of repeated blood transfusions include transfusion reactions, allergic reactions, hemolytic anemia, transfusion-related acute lung injury, and transfusion-related graft versus host disease and alloimmunization.<sup>12</sup> In the event of alloimmunization, it becomes difficult to find a matched blood and also increases the likelihood of delayed transfusion reactions. However, the main complication from frequent blood transfusions is iron overload.

Iron overload as a result of frequent transfusion results in iron accumulation in the heart, liver, and pituitary gland and can lead to heart failure, cirrhosis, hepatocellular carcinoma, hypothyroidism, hypoparathyroidism, hypogonadism, diabetes, and growth failure.<sup>13</sup> Primary treatment for iron overload is chelation therapy (desferrioxamine, deferasirox, deferiprone) and is typically initiated after 10 to 20 transfusions or when the serum ferritin level rises above 1000 mcg/L.<sup>14</sup> Chelation therapy is associated with side effects such as hearing problems, bone growth retardation and local reactions, gastrointestinal symptoms, arthralgia, and neutropenia. Another limitation of chelation therapy is lack of adherence when infused therapies are used as compared to higher adherence for patients taking oral therapy.<sup>15</sup>

Hematopoietic stem cell transplant is the only curative treatment with cure rates ranging from 80% to 90% in children who receive human leukocyte antigen-identical sibling transplant.<sup>16</sup> Cure rates in adults are lower with a reported range of 65% to 70%.<sup>17</sup> While the cure rates are high, the main limiting factor for hematopoietic stem cell transplant is lack of a compatible donor. Fewer than 25% of patients have compatible related or unrelated donors, and transplants with mismatched donors or unrelated umbilical cord blood have a lower success rate.<sup>18</sup> Complications from hematopoietic stem cell transplant include mucositis, infection, graft failure, and graft versus host disease. If available, hematopoietic stem cell transplant should be offered to patients early in the disease course, prior to the onset of iron overload.<sup>14</sup>

There are no randomized trials comparing hematopoietic stem cell transplant with medical therapy for transfusion-dependent thalassemia.<sup>19</sup> Only a 2017 retrospective case-control study has been published, showing no statistically different overall survival with transplantation versus conventional medical therapy (eg, transfusions and iron chelation).<sup>17</sup> The Center for International Blood and Marrow Transplant Research reported the results of a retrospective cohort of 1110 individuals with  $\beta$ -thalassemia who received a hematopoietic stem cell transplant between 2000 and 2016. The median age at transplantation was 6 years (range: 1 to 25 years), 61% received transplants with grafts from HLA-matched related donors, 7% from HLA-mismatched related donors, 23% from HLA-matched unrelated donors, and 9% from HLA-mismatched unrelated donors. The results are summarized in Table 2.

**Table 2. Outcomes of Retrospective Cohort of Individuals Who Received Hematopoietic Stem Cell Transplant for  $\beta$ -Thalassemia**

Outcome	Matched Sibling	Matched Unrelated	Mismatched Relative	Mismatched Unrelated
5-year survival	89% (n=677)	87% (n=252)	73% (n=78)	83% (n=103)
Graft failure	8.6% (n=677)	5.2% (n=252)	21.8% (n=78)	10.7% (n=103)
Grade 2-4 acute GVHD	11.9% (n=674)	21.5% (n=251)	35.1% (n=77)	19.8% (n=101)
Chronic GVHD	8.3% (n=627)	8.4% (n=249)	20% (n=70)	23.8% (n=101)

<sup>a</sup> Matched relative representative of matched sibling in this study.  
GVHD: graft-versus-host disease.

## Description

$\beta$ -thalassemia is a genetic hemoglobinopathy that results from defects in  $\beta$ -globin synthesis leading to reduced synthesis or absence of  $\beta$ -globin chains causing impaired production of hemoglobin. The clinical presentation is that of anemia which requires transfusion and multiple downstream sequelae from iron overload. It is estimated that at least 1000 people in the United States have transfusion-dependent  $\beta$ -thalassemia. Betibeglogene autotemcel contains autologous CD34+ hematopoietic stem cells in which functional copies of a modified form of the  $\beta$ -globin gene ( $\beta$ A-T87Q-globin gene) have been added. Once the hematopoietic stem cells reengineered with  $\beta$ A-T87Q are infused, they engraft in the bone marrow and differentiate to produce red blood cells containing  $\beta$ A-T87Q gene that will produce HbAT87Q protein (functional gene therapy-derived hemoglobin) at levels that may eliminate or significantly reduce the need for transfusions.

## Summary of Evidence

For individuals with transfusion-dependent  $\beta$ -thalassemia who receive betibeglogene autotemcel, the evidence includes 2 single-arm studies: HGB-207 (Northstar-2) and HGB-212 (Northstar-3). The Northstar-2 trial enrolled non-  $\beta$ 0 $\beta$ 0 genotype (less severe phenotype) while Northstar-3 trial enrolled  $\beta$ -thalassemia patients with either a  $\beta$ 0 or  $\beta$ + IVS1 110 (G>A) variant (severe phenotype) at both alleles of the HBB gene. Relevant outcomes are change in disease status, quality of life, hospitalizations, medication use, treatment-related morbidity and treatment-related mortality. The 2 open-label, phase III, single-arm studies included a total of 41 individuals who received a single intravenous infusion of betibeglogene autotemcel. Of the 41 participants, 36 participants in whom transfusion independence was evaluable were included in the efficacy analysis. Transfusion independence was achieved in 89% (95% CI, 74% to 97%) of study participants. Limitations include a small sample size and limited duration of

follow-up. There is uncertainty regarding the durability of effect over a longer time period. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect. The small sample size creates uncertainty around the estimates of some of the patient-important outcomes, particularly adverse events. Some serious harms are likely rare occurrences and, as such, may not be observed in small trials. While most of the serious adverse events were attributable to known risks associated with myeloablative conditioning, uncertainty still remains about the degree of risk with betibeglogene autotemcel infusion in real-world practice. Insertional oncogenesis has been identified as a potential risk with transgene integration. There has been no evidence of insertional oncogenesis and no malignancies in the trials of betibeglogene autotemcel. However, cases of myelodysplastic syndrome and acute myeloid leukemia have been reported in gene therapy trials that use a lentiviral vector to treat other conditions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

## Policy History

Date	Action
3/2024	Updated to add a note for Outcomes-based contracts.
10/13/2022	Policy created with literature review through August 17, 2022. The use of betibeglogene autotemcel is considered medically necessary for individuals with transfusion dependent beta thalassemia when certain conditions are met. Effective 10/13/2022.

## Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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