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Betibeglogene Autotemcel

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INSTRUCTIONS FOR USE

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Overview

This policy supports medical necessity review for the gene therapy, betibeglogene autotemcel (Zynteglo™) intravenous infusion.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Gene Therapy coverage varies across plans. Refer to the customer's benefit plan document for coverage details.

Medical Necessity Criteria

Betibeglogene autotemcel (Zynteglo) is considered medically necessary for the treatment of transfusion dependent Beta Thalassemia when the individual meets ALL of the following criteria:

- 1. 4 years of age to 50 years of age
2. Documentation of ONE of the following genotypes confirmed by DNA analysis (i.e. beta-globin gene [HBB] sequencing) (A or B):

A. Non- β^0/β^0

Examples: β^0/β^+ , β^E/β^0 , and β^+/β^+ .

B. β^0/β^0

Other examples: β^0/β^+ (IVS-I-110) and β^+ (IVS-I-110)/ β^+ (IVS-I-110).

3. Documentation of transfusion dependence defined by meeting **ONE** of the following:
 - A. Received transfusions of at least 100 mL per kg of body weight per year of packed red cells (pRBCs) for the past 2 years
 - B. Received eight or more transfusions of pRBCs per year for the past 2 years
4. According to the prescriber, is unable to receive stem cell transplant due to no matching or unwilling Human Leukocyte Antigen (HLA)-Matched Family Donor
5. Documentation of **ALL** of the following:
 - A. Estimated glomerular filtration rate (eGFR) of at least 70 mL/min/1.73 m²
 - B. Recent (i.e. within 30 days) white blood cell count of at least $3 \times 10^9/L$
 - C. Recent (i.e. within 30 days) platelet count of at least $100 \times 10^9/L$
 - D. Diffusion capacity of carbon monoxide greater than 50% of predicted
 - E. Prior to collection of cells for manufacturing, is negative for the following (i and ii):
 - i. Human Immunodeficiency virus 1 and 2
 - ii. Human T-lymphotropic virus 1 and 2
 - F. Evaluated for AND does not have evidence of severe iron overload

Examples of severe iron overload could include abnormal myocardial iron results ([a T2-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec], high liver iron concentration [at least 15.5 mg/g]), liver biopsy result suggesting abnormalities, or clinical evidence of organ damage (e.g., endocrine comorbidities) within last 6 months.*

- G. **ONE** of the following:
 - i. If 16 years of age or older, has a Karnofsky performance status score of at least 80%
 - ii. If less than 16 years of age, has a Lansky performance status score of at least 80%
- H. Adequate cardiac function as evidenced by a left ventricular ejection fraction greater than 40%
6. According to the prescriber, does **NOT** have any of the following:
 - A. Active bacterial, viral, fungal or parasitic infection
 - B. Prior or current malignancy or myeloproliferative disorder

This does not include adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin.

- C. Familial cancer syndrome or a history of such in their immediate family
- D. Uncorrected bleeding disorder
- E. Advanced liver disease

Examples include evidence of cirrhosis and/or persistent alanine aminotransferase, aspartate transferase or direct bilirubin values greater than three times the upper limit of normal.

7. According to the prescriber, hematopoietic stem cell transplantation procedure is appropriate for the individual as required to receive Zynteglo gene therapy
8. Medication is prescribed by a hematologist and/or a stem cell transplant specialist

Dosing for transfusion dependent Beta Thalassemia. The recommended dose of Zynteglo is a single dose intravenous infusion which contains a minimum of 5.0×10^6 CD34+ cells/kg of body weight.

Authorization Duration

Authorization is for a one-time treatment for 6 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

- 1. Concurrent Use with Reblozyl** (luspatercept-aamt subcutaneous injection). Reblozyl was not utilized with Zynteglo in the pivotal trials.
- 2. Prior Hematopoietic Stem Cell Transplantation.** Patients who had received a prior hematopoietic stem cell transplantation were not allowed to participate in the pivotal clinical trials involving Zynteglo.
- 3. Prior Receipt of Gene Therapy.** Prior receipt of gene therapy was a reason for patient exclusion in the two pivotal trials.

Coding

- 1) This list of codes may not be all-inclusive.
- 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics

Background

OVERVIEW

Zynteglo is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of adult and pediatric patients with β -thalassemia who require regular red blood cell (RBC) transfusions.¹ The efficacy and safety of Zynteglo in children < 4 years of age have not been established; no data are available in this population. Zynteglo is given as a single dose which contains a minimum of 5.0×10^6 CD34+ cells/kg of body weight. The median dose of Zynteglo in the pivotal trials was 9.4×10^6 CD34+ cells/kg.

Disease Overview

The condition of β -thalassemia is a group of recessively inherited blood disorders caused by β -globin gene mutations that either reflect a reduced (β^+) or relative lack (β^0) of production of functional β -globin.² The attenuated or lack of hemoglobin (Hb) results in chronic anemia of varying degrees of severity and insufficient delivery of oxygen to the body. Those with severe anemia may require lifelong RBC transfusions and regular iron chelation to prevent iron overload. The extremely low Hb levels can lead to many types of symptoms and health-related issues (e.g., dizziness, weakness, fatigue, increased cardiac effort, tachycardia, poor growth) or ineffective erythropoiesis (e.g., bone changes, massive splenomegaly). An estimated 3,000 patients in the US have β -thalassemia and slightly less than one-half of the patients are dependent on RBC transfusions.

Clinical Efficacy

The efficacy of Zynteglo was evaluated in two ongoing, open-label, 2-year, single-arm, Phase III trials that involved patients ≤ 50 years of age with transfusion-dependent β -thalassemia (NORTHSTAR-2 and NORTHSTAR-3) who received one dose of Zynteglo.^{1,3} All patients underwent mobilization of stem cells (with granulocyte colony-stimulating factor and Mozobil[®] [plerixafor subcutaneous injection]) and pre-treatment myeloablative conditioning with busulfan prior to treatment with Zynteglo. NORTHSTAR-2 (n = 23) involved patients who had a non- β^0/β^0 genotype. NORTHSTAR 3 (n = 18) involved patients who had a β^0/β^0 or non- β^0/β^0 genotype. In NORTHSTAR-2, 91% of patients obtained transfusion independence, the primary endpoint.^{1,3} Among the patients who obtained transfusion independence, the median weighted average Hb during transfusion independence was 11.8 g/dL.¹ In NORTHSTAR-3, transfusion independence was achieved by 86% of patients.¹ Among the patients who obtained transfusion independence, the median weighted average Hb during transfusion independence was 10.2 g/dL.¹ The median time for the last RBC transfusion prior to transfusion independence after administration of Zynteglo was slightly under 1 month in both trials. In total, 29 patients from NORTHSTAR-2 and NORTHSTAR 3 enrolled in a long-term extension. Data suggest durable results regarding transfusion independence as these two studies have had follow up for over 24 months.

Dosage and Administration

For autologous use only. For intravenous use only.

- Patients are required to undergo hematopoietic stem cell (HSC) mobilization followed by apheresis to obtain CD34+ cells for Zynteglo manufacturing
- Dosing of Zynteglo is based on the number of CD34+ cells in the infusion bag(s) per kg of body weight
- The minimum recommended dose is 5.0×10^6 CD34+ cells/kg.
- Full myeloablative conditioning must be administered before infusion of Zynteglo
- Prophylaxis for hepatic veno-occlusive disease (VOD) is recommended.
- Prophylaxis for seizures should be considered
- Verify that the patient's identity matches the unique patient identification information on the Zynteglo infusion bag(s) prior to infusion
- Do not sample, alter, or irradiate Zynteglo
- Do not use an in-line blood filter or an infusion pump
- Administer each infusion bag of Zynteglo via intravenous infusion over a period of less than 30 minutes

Dosage Forms and Strengths

- Zynteglo is a cell suspension for intravenous infusion
- A single dose of Zynteglo contains a minimum of 5.0×10^6 CD34+ cells/kg of body weight, in one or more infusion bags

Guidelines

Guidelines have not addressed Zynteglo post approval in the US. In 2021, the Thalassemia International Federation published guidelines for the management of transfusion-dependent thalassemia.⁴

- **Chelation therapy** was cited as an effective treatment modality in improving survival, decreasing the risk of heart failure, and decreasing morbidities from transfusional-induced iron overload. The optimal chelation regimen should be individualized and will vary among patients and their clinical status.
- **Allogeneic hematopoietic stem cell transplant (HSCT)** should be offered to patients with β -thalassemia at an early age, before complications due to iron overload have developed if a human leukocyte antigen (HLA) identical sibling is available. In some clinical circumstances, a matched unrelated donor can be adequate.
- **Reblozyl[®]** (luspatercept-aamt subcutaneous injection), an erythroid maturation agent, can be considered for patients ≥ 18 years of age who require regular RBC transfusions.
- **Zynteglo**, when available, may be an option for selected patients. Examples include young with a β^+ genotype who do not have an HLA-compatible sibling donor. Also, Zynteglo can be considered in patients with a β^+ genotype who do not have severe comorbidities and are at risk or ineligible to undergo allogeneic HSCT but can otherwise undergo an autologous gene therapy procedure with an acceptable risk.

References

1. Zynteglo™ intravenous infusion [prescribing information]. Somerville, MA: Bluebird Bio; August 2022.
2. Taher AT, Musallam KM, Cappellini MD, et al. β -thalassemias. *N Engl J Med*. 2021;384:727-743.
3. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene autotemcel gene therapy for non- β^0/β^0 genotype β -thalassemia. *N Engl J Med*. 2022;386:417-427.
4. Farmakis D, Porter J, Taher A, et al, for the 2021 TIF Guidelines Taskforce. 2021 Thalassaemia International Federation guidelines for the management of transfusion-dependent thalassaemia. *Hemasphere*. 2022;6:8(e732).

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