

**POLICY:** Hematology – Gene Therapy – Zynteglo

- Zynteglo™ (betibeglogene autotemcel intravenous infusion – Bluebird Bio)

**EFFECTIVE DATE:** 01/15/2023**LAST REVISION DATE:** 11/01/2023**COVERAGE CRITERIA FOR: ALL UCARE PLANS**

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**OVERVIEW**

Zynteglo is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of adult and pediatric patients with  $\beta$ -thalassemia who require regular red blood cell (RBC) transfusions.<sup>1</sup> 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  $5.0 \times 10^6$  CD34+ cells/kg of body weight. The median dose of Zynteglo in the pivotal trials was  $9.4 \times 10^6$  CD34+ cells/kg.

**Disease Overview**

The condition of  $\beta$ -thalassemia is a group of recessively inherited blood disorders caused by  $\beta$ -globin gene mutations that either reflect a reduced ( $\beta^+$ ) or relative lack ( $\beta^0$ ) of production of functional  $\beta$ -globin.<sup>2</sup> 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  $\beta$ -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  $\leq 50$  years of age with transfusion-dependent  $\beta$ -thalassemia (NORTHSTAR-2 and NORTHSTAR-3) who received one dose of Zynteglo.<sup>1,3</sup> 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- $\beta^0/\beta^0$  genotype. NORTHSTAR 3 (n = 18) involved patients who had a  $\beta^0/\beta^0$  or non- $\beta^0/\beta^0$  genotype. In NORTHSTAR-2, 91% of patients obtained transfusion independence, the primary endpoint. Among the patients who obtained transfusion independence, the median weighted average Hb during transfusion independence was 11.8 g/dL.<sup>1</sup> In NORTHSTAR-3, transfusion independence was achieved by 86% of patients. Among the patients who obtained transfusion independence, the median weighted average Hb during transfusion independence was 10.2 g/dL. 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.

**Guidelines**

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

- **Chelation therapy** was cited as an effective treatment modality in improving survival, decreasing the risk of heart failure, and decreasing morbidities from transfusion-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  $\beta$ -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**<sup>®</sup> (luspatercept-aamt subcutaneous injection), an erythroid maturation agent, can be considered for patients  $\geq 18$  years of age who require regular RBC transfusions.
- **Zynteglo**, when available, may be an option for selected patients. Examples include young patients (12 to 17 years of age) with a  $\beta^+$  genotype who do not have an HLA-compatible sibling donor. Also, Zynteglo can be considered in patients 17 to 55 years of age with a  $\beta^+$  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.

## POLICY STATEMENT

Prior Authorization is recommended for benefit coverage of Zynteglo. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Zynteglo as well as the specialized training required for administration of Zynteglo, approval requires Zynteglo to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for one dose per lifetime. The approval duration is 6 months to allow for an adequate time frame to prepare and administered one dose of therapy. For certain criteria, verification is required as noted by **[verification in claims history required]**. In the criteria for Zynteglo, as appropriate, an asterisk (\*) is noted next to the specified gender. In this context, the specified gender is defined as follows: females/males are defined as individuals with the biological traits of a woman/man, regardless of the individual's gender identity or gender expression.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with eviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to [Embarc@eviCore.com](mailto:Embarc@eviCore.com) prior to completing the review.

**Documentation:** Documentation is required for use of Zynteglo where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to chart notes, laboratory tests, claims records, and/or other information.

**Automation:** None.

## RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Zynteglo is recommended in those who meet the following criteria:

### FDA-Approved Indication

1. **Beta Thalassemia.** Approve for a one-time (lifetime) dose if the patient meets the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q, and R):

- A) Patient is  $\geq 4$  to  $\leq 50$  years of age; AND
- B) Patient is transfusion dependent defined by meeting one of the following (i or ii) **[documentation required]**:
  - i. Receipt of transfusions of  $\geq 100$  mL per kg of body weight of packed red cells per year in the 2 years preceding enrollment **[documentation required]**; OR
  - ii. Patient has received transfusions eight or more times per year in the 2 years before enrollment **[documentation required]**; AND
- C) Patient has one of the following genotypes as confirmed by DNA analysis (i or ii) **[documentation required]**:
  - i. Non- $\beta^0/\beta^0$  genotype **[documentation required]**; OR  
Note: Examples include  $\beta^0/\beta^+$ ,  $\beta^E/\beta^0$ , and  $\beta^+/ \beta^+$ .
  - ii.  $\beta^0/\beta^0$  genotypes **[documentation required]**; AND  
Note: Other examples include  $\beta^0/\beta^{+(IVS-I-110)}$  and  $\beta^{+(IVS-I-110)}/\beta^{+(IVS-I-110)}$ .
- D) Patient does not currently have an active bacterial, viral, fungal, or parasitic infection; AND
- E) According to the prescribing physician, hematopoietic stem cell transplantation is appropriate for the patient; AND
- F) Patient meets all of the following (i, ii, iii, iv, and v)
  - i. Patient will undergo mobilization, apheresis, and myeloablative conditioning; AND
  - ii. The prescribing physician confirms that the hemoglobin level is or will be  $\geq 11.0$  g/dL within 30 days prior to the following clinical scenarios (a and b):
    - a) Prior to mobilization; AND
    - b) Before myeloablative conditioning; AND
  - iii. A granulocyte-colony stimulating factor product and a hematopoietic stem cell mobilizer will be utilized for mobilization; AND  
Note: Filgrastim products are examples of a granulocyte-colony stimulator factor therapy and Mozobil (plerixafor subcutaneous injection) is an example of a hematopoietic stem cell mobilizer.
  - iv. Busulfan will be used for myeloablative conditioning; AND
  - v. Patient meets both of the following (a and b):
    - a) Patient is not receiving iron chelation therapy or this therapy will be stopped at least 7 days prior to myeloablative conditioning; AND  
Note: Examples of iron chelators used for this condition include deferoxamine injection; deferiprone tablets or solution; and deferasirox tablets.
    - b) Use of iron chelators will be avoided for 6 months after infusion of Zynteglo; AND
- G) Patient has received or is planning to receive prophylaxis for hepatic veno-occlusive disease/hepatic sinusoidal obstruction syndrome before myeloablative conditioning with busulfan; AND  
Note: Examples of medications used include ursodeoxycholic acid or Defitelio (defibrotide intravenous infusion).
- H) Females\* of reproductive potential must have the prescribing physician confirm the following (i and ii):
  - i. A negative serum pregnancy test was or will be obtained prior to the start of mobilization and re-confirmed prior to conditioning procedures, as well as before Zynteglo administration; AND
  - ii. The patient will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Zynteglo; AND
- I) Males\* must have the prescribing physician confirm that the patient will be using an effective method of contraception from the start of mobilization through at least 6 months after administration of Zynteglo; AND
- J) Prior to collection of cells for manufacturing, screening is negative for the following (i and ii):
  - i. Human T-lymphotropic virus 1 and 2 **[documentation required]**; AND

- ii. Human immunodeficiency virus 1 and 2 **[documentation required]**; AND
- K) Patient meets one of the following (i or ii):
  - i. Patients  $\geq 16$  years of age have a Karnofsky performance status score of  $\geq 80$  **[documentation required]**; OR
  - ii. Patients  $< 16$  years of age have a Lansky performance status score of  $\geq 80$  **[documentation required]**; AND
- L) Patient meets both of the following (i and ii):
  - i. Within 30 days before intended receipt of Zynteglo, the white blood cell count was  $\geq 3 \times 10^9/L$  **[documentation required]**; AND
  - ii. Within 30 days before intended receipt of Zynteglo, the platelet count was  $\geq 100 \times 10^9/L$  **[documentation required]**; AND
- M) Patient meets both of the following (i and ii):
  - i. Patient has been evaluated for the presence of severe iron overload **[documentation required]**; AND
  - ii. Patient does not have evidence of severe iron overload; AND  
Note: 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 ( $\geq 15.5$  mg/g); liver biopsy results suggest abnormalities; or clinical evidence of organ damage (e.g., endocrine comorbidities).
- N) Patient does not have any of the following (i, ii, iii, iv, v, and vi):
  - i. Prior or current malignancy or myeloproliferative disorder; AND  
Note: This does not include adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin.
  - ii. Familial cancer syndrome or a history of such in their immediate family; AND
  - iii. An estimated glomerular filtration rate of  $< 70$  mL/min/1.73 m<sup>2</sup> **[documentation required]**; AND
  - iv. Uncorrected bleeding disorder; AND
  - v. A diffusion capacity of carbon monoxide  $< 50\%$  of predicted **[documentation required]**; AND
  - vi. Advanced liver disease; AND  
Note: Examples include evidence of cirrhosis and/or persistent alanine aminotransferase, aspartate aminotransferase, or direct bilirubin values greater than three times the upper limit of normal; AND
- O) Patient meets one of the following (i or ii):
  - i. Patient does not have a Human Leukocyte Antigen (HLA)-Matched Family Donor; OR
  - ii. Patient has a Human Leukocyte Antigen (HLA)-Matched Family Donor but the individual is not able or is unwilling to donate; AND
- P) Patient has not received Zynteglo in the past **[verification in claims history required]**; AND  
Note: Verify through claims history that the patient has not previously received Zynteglo AND, if no claim for Zynteglo is present, the prescribing physician confirms that the patient has not previously received Zynteglo.
- Q) Medication is prescribed by a hematologist and/or a stem cell transplant specialist; AND
- R) Zynteglo is given as a single dose which contains a minimum of  $5.0 \times 10^6$  CD34+ cells/kg of body weight.

\* Refer to the Policy Statement.

**Dosing.** The recommended dose of Zynteglo is a single intravenous infusion which contains a minimum of  $5.0 \times 10^6$  CD34+ cells/kg of body weight.

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### CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zynteglo is not recommended in the following situations:

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.**  
**Note:** Prescribing physician must confirm that the patient has not received a 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.
4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

### REFERENCES

1. Zynteglo™ intravenous infusion [prescribing information]. Somerville, MA: Bluebird Bio; August 2022.
2. Taher AT, Musallam KM, Cappellini MD, et al.  $\beta$ -thalassemias. *N Engl J Med.* 2021;384:727-743.
3. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene autotemcel gene therapy for non- $\beta^0/\beta^0$  genotype  $\beta$ -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 thalassemia. *Hemasphere.* 2022;6:8(e732).

## HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	09/28/2022
Selected Revision	The phrase “Gene Therapy” was added to the header. In addition, the following change was made: <b>Beta Thalassemia:</b> Criteria changed from “Patient has a recent white blood cell count $\geq 3 \times 10^9/L$ [documentation required]”; OR “Patient has a recent platelet count $\geq 100 \times 10^9/L$ [documentation required]” to requiring both criterion be met.	10/19/2022
Annual Revision	In the Policy Statement [attestation required by physician] was removed from this policy. It was added that for certain criteria, verification is required as noted by [verification in claims history required]. In addition, the following changes were made: 1. <b>Beta Thalassemia:</b> The phrase “as determined by the prescribing physician” was removed from the requirement regarding that the patient is without an active infection (bacterial, viral, fungal, or parasitic). The phrase “plans to” was changed to “will” to be more directive in the requirement that the patient undergoes mobilization, apheresis, and myeloablative conditioning. Regarding the requirement that Mozobil will be utilized for mobilization, this was changed to the more broad term “hematopoietic stem cell mobilizer” and Mozobil was added to the Note stating that it is an example of a hematopoietic stem cell mobilizer. In the requirement that use of iron chelators will be avoided for 6 months after infusion of Zynteglo, the [attestation required by physician] was removed. The word “recent” was replaced with the phrase “within 30 days before intended receipt of Zynteglo” regarding meeting thresholds for white blood cell count and platelet count. Regarding the requirement that the patient does not have evidence of severe iron overload, the [attestation required by physician] was removed. It was added that the patient has not received Zynteglo in the past, with [verification in claims history required]. Dosing was added in an additional section with the other standard requirements for alignment with similar policies; dosing requirements were always present with Zynteglo for this policy. 2. <b>Conditions Not Recommended for Approval:</b> The [attestation required by physician] was removed from the exclusion regarding prior hematopoietic stem cell transplantation. A Note was added that the prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.	11/01/2023