

Medical Policy: Zynteglo® (betibeglogene autotemcel)

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.368	December 14, 2023	December 2, 2022

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The treating physician or primary care provider must submit to EmblemHealth, or ConnectiCare, as applicable (hereinafter jointly referred to as “EmblemHealth”), the clinical evidence that the member meets the criteria for the treatment or surgical procedure. Without this documentation and information, EmblemHealth will not be able to properly review the request preauthorization or post-payment review. The clinical review criteria expressed below reflects how EmblemHealth determines whether certain services or supplies are medically necessary. This clinical policy is not intended to pre-empt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Health care providers are expected to exercise their medical judgment in rendering appropriate care.

EmblemHealth established the clinical review criteria based upon a review of currently available clinical information (including clinical outcome studies in the peer reviewed published medical literature, regulatory status of the technology, evidence-based guidelines of public health and health research agencies, evidence-based guidelines and positions of leading national health professional organizations, views of physicians practicing in relevant clinical areas, and other relevant factors). EmblemHealth expressly reserves the right to revise these conclusions as clinical information changes and welcomes further relevant information. Each benefit program defines which services are covered. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered and/or paid for by EmblemHealth, as some programs exclude coverage for services or supplies that EmblemHealth considers medically necessary.

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Definitions

Zynteglo, an autologous hematopoietic stem cell-based gene therapy, is indicated for the treatment of β -thalassemia in adults and pediatric patients with who require regular red blood cell (RBC) transfusions.

Length of Authorization

Coverage will be provided for one treatment course (1 dose of Zynteglo) and may not be renewed

Dosing Limits [Medical Benefit]

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.

Max Units:

1. A single dose of Zynteglo containing a minimum of 5.0×10^6 CD34+ cells/kg of body weight, in one or more infusion bags

Guideline

1. **Beta Thalassemia.** Approve for a one-time (lifetime) dose if the patient meets the following criteria (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, **and** P):
 - A. Patient is ≥ 4 years of age; **AND**
 - B. Patient is transfusion dependent defined by meeting one of the following (i **or** ii):
 - i. Receipt of transfusions of ≥ 100 mL per kg of body weight of packed red cells per year in the 2 years preceding enrollment; **OR**
 - ii. Patient has received transfusions eight or more times per year in the 2 years before enrollment; **AND**
 - C. Patient has one of the following genotypes as confirmed by DNA analysis (i **or** ii):
 - i. Non- β^0/β^0 genotype; **OR**
Note: Examples include β^0/β^+ , β^E/β^0 , and β^+/β^+ .
 - ii. β^0/β^0 genotypes; **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 as determined by the prescribing physician; **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 ≥ 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 Mozobil (plerixafor subcutaneous injection) will be utilized for mobilization; **AND**
Note: Filgrastim products are examples of a granulocyte-colony stimulator factor therapy.
 - 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; **AND**
 - ii. Human immunodeficiency virus 1 and 2; **AND**

- K. Patient meets one of the following (i **or** ii):
 - i. Patients ≥ 16 years of age have a Karnofsky performance status score of ≥ 80 ; **OR**
 - ii. Patients < 16 years of age have a Lansky performance status score of ≥ 80 ; **AND**
- L. Patient meets does not have hypersplenism **AND** meets BOTH of the following (i **and** ii):
 - i. Patient has a within 30 days before intended receipt of Zynteglo white blood cell count $\geq 3 \times 10^9/L$; **AND**
 - ii. Patient has a within 30 days before intended receipt of Zynteglo platelet count $\geq 100 \times 10^9/L$; **AND**
- M. Patient meets both of the following (i **and** ii):
 - i. Patient has been evaluated for the presence of severe iron overload; **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 (≥ 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 m²; **AND**
 - iv. Uncorrected bleeding disorder; **AND**
 - v. A diffusion capacity of carbon monoxide $< 50\%$ of predicted; **AND**
 - vi. Advanced liver disease; **AND**

*Note: 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; **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. Medication is prescribed by a hematologist and/or a stem cell transplant specialist.

Limitations/Exclusions

1. Concurrent Use with Reblozyl (luspatercept-aamt subcutaneous injection).
2. Prior Hematopoietic Stem Cell Transplantation
3. Prior Receipt of Gene Therapy

Dosing and Administration

Mobilization and Apheresis

1. Patients are required to undergo HSC mobilization followed by apheresis to obtain CD34+ cells for product manufacturing. The target number of CD34+ cells to be collected is $\geq 12 \times 10^6$ CD34+ cells/kg. (Note: If the minimum dose of 5.0×10^6 CD34+ cells/kg is not met, the patient may undergo additional cycles of mobilization and apheresis, separated by at least 14 days, in order to obtain more cells for additional manufacture. Up to two drug product lots may be administered to meet the target dose.)
2. A back-up collection of CD34+ cells of $\geq 1.5 \times 10^6$ CD34+ cells/kg (if collected by apheresis) or $> 1.0 \times 10^8$ TNC/kg (Total Nucleated Cells, if collected by bone marrow harvest) is required. These cells must be collected from the patient and be cryopreserved prior to myeloablative conditioning. The back-up collection may be needed for rescue treatment if there is:
 - a. Compromise of hematopoietic stem cells or Zynteglo before infusion

- b. Primary engraftment failure
 - c. Loss of engraftment after infusion with Zynteglo
- Note: G-CSF and plerixafor were used for mobilization*

Myeloablative Conditioning

1. Full myeloablative conditioning must be administered before infusion of Zynteglo. Consult prescribing information for the myeloablative conditioning agent(s) prior to treatment.
2. Prophylaxis for hepatic veno-occlusive disease (VOD) is recommended and prophylaxis for seizures should be considered, as appropriate.
3. Do not begin myeloablative conditioning until the complete set of infusion bag(s) constituting the dose of Zynteglo has been received and stored at the treatment center and the availability of the back-up collection is confirmed. After completion of the myeloablative conditioning, allow a minimum of 48 hours of washout before Zynteglo infusion.

Note: busulfan was used for myeloablative conditioning

Administration

1. Verify that the patient’s identity matches the unique patient identification information on the Zynteglo infusion bag(s) prior to infusion.
2. Do not sample, alter, or irradiate Zynteglo.
3. Do not use an in-line blood filter or an infusion pump.
4. Administer each infusion bag of Zynteglo via intravenous infusion over a period of less than 30 minutes. Product must be administered within 4 hours after thawing.

Applicable Procedure Codes

Code	Description
J3590	Unclassified biologics

Applicable NDCs

Code	Description
73554-3111-xx	Zynteglo, 20 mL/infusion bag, overwrap, and metal cassette

ICD-10 Diagnoses

Code	Description
D56.1	Beta thalassemia

Revision History

Company(ies)	DATE	REVISION
EmblemHealth & ConnectiCare	12/14/2023	Annual Review: Initial Criteria: The phrase “plans to” was changed to “will” to be more directive in the requirement that the patient undergoes mobilization, apheresis, and myeloablative conditioning.

		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 counts. This Statement was further modified to include: Patient “does not have hypersplensism” and meets BOTH of the following.
EmblemHealth & ConnectiCare	3/3/2023	Annual Review- Beta Thalassemia: Criteria changed from “Patient has a recent white blood cell count $\geq 3 \times 10^9/L$ ”; OR “Patient has a recent platelet count $\geq 100 \times 10^9/L$ ” to requiring both criterion be met.
EmblemHealth & ConnectiCare	12/2/2022	New Policy

References

1. Zynteglo [package insert]. Somerville, MA; Bluebird bio, Inc: August 2022. Accessed November 2022.
2. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene Autotemcel Gene Therapy for Non- $\beta(0)/\beta(0)$ Genotype β -Thalassemia. N Engl J Med. 2022 Feb 3;386(5):415-427. doi: 10.1056/NEJMoa2113206. Epub 2021 Dec 11