Medical Policy:
Zynteglo® (betibeglogene autotemcel)

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.368	June 20, 2025	December 2, 2022

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 x 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, and O):
   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 $\beta^0/\beta^{+(IVS\text{-}I\text{-}110)}$ and $\beta^{+(IVS\text{-}I\text{-}110)}/\beta^{+(IVS\text{-}I\text{-}110)}$.
   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 myelosuppressive 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 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).*

M. Patient does not have any of the following (i, ii, iii, iv, v **and** vi):
   i. Prior or current malignancy or myeloproliferative disorder or significant immunodeficiency 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**

N. 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**

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

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 ≥ 12×10^6 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 ≥ 1.5×10^6 CD34+ cells/kg (if collected by apheresis) or > 1.0×10^8 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
J3393	Injection, betibeglogene autotemcel, per treatment

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	6/20/2025	Update: Removed from criteria: • Patient has not received a gene therapy for beta-thalassemia in the past [verification in claims history required]; **AND** *Note: If no claim for Zynteglo or Casgevy (exagamglogene autotemcel intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Zynteglo or Casgevy.* • Removed from :Prior to collection of cells for manufacturing, screening is negative for the following" from Hepatitis B virus; **AND** Hepatitis C virus**;** • Current patient body weight has been obtained within 30 days Addition to criteria: • 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).* • Use of myelosuppressive iron chelators will be avoided for 6 months after infusion of Zynteglo. • Familial cancer syndrome or a history of such in their immediate family; **AND** An estimated glomerular filtration rate of < 70 mL/min/1.73 m2; **AND** Uncorrected bleeding disorder; **AND** A diffusion capacity of carbon monoxide < 50% of predicted • Patient meets one of the following (i **or** ii): ▪ Patients ≥ 16 years of age have a Karnofsky performance status score of ≥ 80; **OR** ▪ Patients < 16 years of age have a Lansky performance status score of ≥ 80
EmblemHealth & ConnectiCare	4/9/2025	Annual Review: Updated J code to J3393. Initial Criteria: Added: "Patient has not received a gene therapy for beta-thalassemia in the past [verification in claims history required]; AND *Note: If no claim for Zynteglo or Casgevy (exagamglogene autotemcel intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Zynteglo or Casgevy."* Removed: "Use of iron chelators will be avoided for 6 months after infusion of Zynteglo: AND 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)." Added Hepatitis B and C to the following: "*Prior to collection of cells for manufacturing, screening is negative for the following (i , ii, iii, and, iv): Hepatitis B virus; AND Hepatitis C virus; AND" removed: "Patient meets one of the following (i or ii): Patients ≥ 16 years of age have a Karnofsky performance status score of ≥ 80; OR Patients < 16 years of age have a Lansky performance status score of ≥ 80; AND Patient meets does not have hypersplenism AND meets BOTH of the following (i and ii): Patient has a within 30 days before intended receipt of Zynteglo white blood cell count ≥ 3 x 10^9/L; AND Patient has a within 30 days before intended receipt of Zynteglo platelet count ≥ 100 x 10^9/L; AND" Added "significant immunodeficiency disorder to the following: "Prior or current malignancy or myeloproliferative disorder or significant immunodeficiency disorder; AND" Removed:"Familial cancer syndrome or a history of such in their immediate family; AND An estimated glomerular filtration rate of < 70 mL/min/1.73 m^2; AND Uncorrected bleeding disorder; AND A diffusion capacity of carbon monoxide < 50% of predicted; AND" Added: "Current patient body weight has been obtained within 30 days"
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 ≥ 3 x 109/L"; OR "Patient has a recent platelet count ≥ 100 x 109/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-β(0)/β(0) Genotype β-Thalassemia. N Engl J Med. 2022 Feb 3;386(5):415-427. doi: 10.1056/NEJMoa2113206. Epub 2021 Dec 11