Drug Coverage Policy

Effective Date..... 05/08/2025
Coverage Policy Number IP0486
Policy Title..... Zynteglo

Hematology – Gene Therapy – Zynteglo

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

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Zyntelgo, an autologous hematopoietic stem cell-based gene therapy, is indicated for the treatment of beta-thalassemia in adult and pediatric patients 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 one-time (per lifetime) single dose which contains a minimum of 5.0 x 10^6 cluster of differentiation 34+ (CD34+) cells/kg of body weight. Zynteglo is given as an intravenous infusion. The median dose of Zynteglo in the pivotal trials was 9.4 x 10^6 CD34+ cells/kg. The manufacturing time (which includes quality control) can take up to 6 months. Patients need to undergo mobilization and apheresis procedures, as well as myeloablative conditioning prior to Zynteglo infusion.

Zynteglo is prepared from the patient's own hematopoietic stem cells, which are obtained via apheresis procedure(s). Zynteglo is a $\beta^{A\text{-}T87Q}$-globin gene therapy comprised of autologous CD34+ cells, containing hematopoietic stem cells transduced with BB305 lentiviral vector (LVV) encoding $\beta^{A\text{-}T87Q}$-globin. Zynteglo adds functional copies of a modified form of the β-globin gene ($\beta^{A\text{-}T87Q}$-globin gene) into individual hematopoietic stem cells.

Disease Overview
The condition of beta-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 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 ≤ 50 years of age with transfusion-dependent beta-thalassemia (NORTHSTAR-2 and NORTHSTAR-3) who received one dose of Zynteglo.[1,3,4] 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. 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. 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 or Casgevy post approval in the US. In 2021, the Thalassaemia International Federation published guidelines for the management of transfusion-dependent thalassemia.[5]

- **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®** (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 patients (12 to 17 years of age) with a β^+ 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 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.

Coverage Policy

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 a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. The approval duration is 1 year to allow for an adequate time frame to prepare and administer one dose of therapy. If claims history is available, verification is required for certain criteria, as noted by **[verification in claims history required]**. For dosing criteria, verification of the appropriate weight-based dosing is required by the Medical Director as noted by **[verification required]**. In the criteria for Zynteglo, as appropriate, the symbol (†) 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.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information.

Zynteglo is considered medically necessary when the following criteria are met:

FDA-Approved Indication

1. **Transfusion-Dependent Beta-Thalassemia.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (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 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.
   - **C)** According to the prescribing physician, a hematopoietic stem cell transplantation is appropriate for the patient; AND
   - **D)** Patient meets ONE of the following (i or ii):
     - **i.** Patient does not have a Human Leukocyte Antigen (HLA)-matched donor; OR

ii. Patient has an HLA-matched donor, but the individual is not able or is not willing to donate; AND

E) Patient has ONE of the following genotypes as confirmed by genetic testing (i or ii):
- **i.** Non-β^0/β^0 genotype **[documentation required]**; OR
  Note: Examples include β^0/β^+, β^E/β^0, and β^+/β^+.
- **ii.** β^0/β^0 genotypes **[documentation required]**; AND
  Note: Other examples include $\beta^0/\beta^{+(IVS\text{-}I\text{-}110)}$ and $\beta^{+(IVS\text{-}I\text{-}110)}/\beta^{+(IVS\text{-}I\text{-}110)}$.

F) Patient is transfusion-dependent, as defined by meeting ONE of the following (i or ii):
- **i.** Receipt of transfusions of ≥ 100 mL of packed red cells per kg of body weight per year in the previous 2 years **[documentation required]**; OR
- **ii.** Receipt of transfusions eight or more times per year in the previous 2 years **[documentation required]**; AND

G) 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 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 mg/g), liver biopsy results suggest abnormalities, or clinical evidence of organ damage (e.g., endocrine comorbidities).

H) Patient does not currently have an active bacterial, viral, fungal, or parasitic infection; AND

I) Patient does not have any of the following (i and ii):
- **i.** Prior or current malignancy, 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.** Advanced liver disease **[documentation required]**; AND
  Note: Examples include alanine transaminase or aspartate transaminase greater than three times upper limit of normal, direct bilirubin value greater than three times upper limit of normal, active hepatitis, extensive bridging fibrosis, or cirrhosis.

J) According to the prescribing physician, patient will have been discontinued from iron chelation therapy for 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.

K) According to the prescribing physician, patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient will undergo mobilization, apheresis, and myeloablative conditioning; AND
- **ii.** 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 stimulating factor therapy and Mozobil (plerixafor subcutaneous injection) is an example of a hematopoietic stem cell mobilizer.
- **iii.** Busulfan will be used for myeloablative conditioning; AND
- **iv.** Total hemoglobin level is ≥ 11.0 g/dL at BOTH of the following timepoints (a and b):
  - **a)** Prior to mobilization; AND
  - **b)** Prior to myeloablative conditioning; AND

L) Patient screening is negative for ALL the following (i, ii, iii, and iv):
- **i.** Human immunodeficiency virus-1 and -2 **[documentation required]**; AND
- **ii.** Hepatitis B virus **[documentation required]**; AND
- **iii.** Hepatitis C virus **[documentation required]**; AND
- **iv.** Human T-lymphotropic virus-1 and -2 **[documentation required]**; AND

M) According to the prescribing physician, a patient of reproductive potential meets ONE of the following (i or ii):
- **i.** A female† of reproductive potential meets BOTH of the following (a and b):

a) A negative serum pregnancy test will be confirmed prior to the start of mobilization and re-confirmed prior to myeloablative conditioning; AND

b) Patient will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Zynteglo; OR

ii. A male† of reproductive potential will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Zynteglo; AND

N) The medication is prescribed by a hematologist or a stem cell transplant specialist physician; AND

O) Current patient body weight has been obtained within 30 days **[documentation required]**; AND

P) If criteria A through O are met, approve one dose of Zynteglo by intravenous infusion to provide a one-time (per lifetime) single dose which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight **[verification required]**.

† Refer to the Policy Statement.

Dosing. The recommended dose of Zynteglo is one dose by intravenous infusion to provide a one-time (per lifetime) single dose which contains a minimum of 5.0 x 10^6 CD34+ cells/kg of body weight.

Conditions Not Covered

Zynteglo for any other use is considered not medically necessary including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Prior Hematopoietic Stem Cell Transplantation**.
   Note: Prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.
   Zynteglo has not been studied in a patient who has received a prior allogeneic or autologous hematopoietic stem cell transplant. Treatment with Zynteglo is not recommended.

2. **Prior Receipt of Gene Therapy**. Prior receipt of gene therapy was a reason for patient exclusion in the two pivotal trials.

3. **Concurrent Use with Reblozyl** (luspatercept-aamt subcutaneous injection). Reblozyl was not utilized with Zynteglo in the pivotal trials assessing Zynteglo in patients with transfusion-dependent beta-thalassemia.

Coding Information

Note: 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
J3393	Injection, betibeglogene autotemcel, per treatment

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. Kwiatowski JL, Walters MC, Hongeng S, et al. Betibeglogene autotemcel gene therapy in patients with transfusion-dependent, severe genotype β-thalassaemia (HGB-212): a non-randomized, multicenter, single-arm, open-label, single-dose, phase 3 trial. *Lancet*. 2024;404(10468):2175-2186.
5. 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).

Revision Details

Type of Revision	Summary of Changes	Date
Selected Revision	**Transfusion-Dependent Beta-Thalassemia:** The upper age threshold (< 51 years of age) was removed; the lower age threshold remains: Patient is ≥ 4 years of age. In the Note for the criterion regarding evidence of severe iron overload, the threshold for high liver iron concentration, ≥ 15.5 mg/g, was changed to ≥ 15 mg/g to align with labeling.	10/17/2024
Early Annual Revision	**Transfusion-Dependent Beta-Thalassemia:** The word "cellular" was removed from the requirement regarding screening for certain viruses prior to collection of cells for manufacturing. The criterion regarding females/males of reproductive potential was clarified that this pertains only to a patient of reproductive potential.	2/27/2025
Selected Revision	**Transfusion-Dependent Beta-Thalassemia:** The qualifier "Prior to collection of cells for manufacturing" was removed from the requirement regarding screening for certain viruses and the word "Patient" was added. The new criterion now reads: "Patient screening is negative for ALL of the following…".	05/08/2025

The policy effective date is in force until updated or retired.