PRIOR AUTHORIZATION POLICY

POLICY: Hematology – Gene Therapy – Zynteglo Prior Authorization Policy
- Zynteglo™ (betibeglogene autotemcel intravenous infusion – Bluebird Bio)

REVIEW DATE: 03/20/2024; selected revision 09/25/2024

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. Casgevy™ (exagamglogene autotemcel intravenous infusion), an autologous hematopoietic stem cell-based gene therapy, is indicated for the treatment of transfusion-dependent beta-thalassemia in patients ≥ 12 years of age.[5] Casgevy is also indicated for the treatment of sickle cell disease in patients ≥ 12 years of age with recurrent vaso-occlusive crises. Casgevy is also given as a one-time (per lifetime) single dose.

Zynteglo is given as a one-time (per lifetime) single dose which contains a minimum of 5.0 x 10^6 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] 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.[4]

- **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.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zynteglo. Approval is recommended for those who meet the Criteria 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 timeframe 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 the 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. 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 prior to completing the review.

Documentation: Documentation is required for use of Zynteglo as 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

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 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) Prior to collection of cells for manufacturing, cellular 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, patient 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 5.0×10^6 CD34+ cells/kg of body weight **[verification required]**.

† Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Zynteglo is not recommended in the following situations:

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.

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. 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 thalassemia. *Hemasphere*. 2022;6:8(e732).
5. Casgevy™ intravenous infusion [prescribing information]. Waltham, MA: Vertex; January 2024.