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Section:	Prescription Drugs	**Effective Date:**	January 1, 2024
Subsection:	Miscellaneous Products	**Original Policy Date:**	September 9, 2022
Subject:	Zynteglo	**Page:**	1 of 4

Last Review Date: December 8, 2023

Zynteglo

Description

Zynteglo (betibeglogene autotemcel)

Background
Zynteglo (betibeglogene autotemcel) adds functional copies of a modified β-globin gene into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with BB305 LVV. After Zynteglo infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce red blood cells (RBCs) containing biologically active $\beta^{A\text{-}T87Q}$-globin (a modified β-globin protein) that will combine with α-globin to produce functional adult hemoglobin (Hb) containing $\beta^{A\text{-}T87Q}$-globin (Hb^{AT87Q}). $\beta^{A\text{-}T87Q}$-globin expression is designed to correct the β/α-globin imbalance in erythroid cells of patients with β-thalassemia and has the potential to increase functional adult HbA and total Hb to normal levels and eliminate dependence on regular packed RBC transfusions (1).

Regulatory Status
FDA-approved indication: Zynteglo is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions (1).

Zynteglo is for autologous use only and for one-time single-dose intravenous use only (1).

Patients are required to undergo HSC mobilization followed by apheresis to obtain CD34+ cells for product manufacturing. It is recommended that patients be maintained at a Hb ≥11 g/dL for at least 30 days prior to mobilization and 30 days prior to myeloablative conditioning.

Granulocyte-colony stimulating factor (G-CSF) and plerixafor were used for mobilization and busulfan was used for myeloablative conditioning (1).

Screening for hepatitis B virus (HBV), hepatitis C virus (HCV), human T-lymphotrophic virus 1 and 2 (HTLV-1/HTLV-2), and human immunodeficiency virus 1 and 2 (HIV-1/HIV-2) should be performed in accordance with clinical guidelines before collection of cells for manufacturing (1).

Full myeloablative conditioning must be administered before infusion of Zynteglo. After completion of the myeloablative conditioning, a minimum of 48 hours washout should be allowed before Zynteglo infusion (1).

Related policies
Exjade Jadenu, Ferriprox

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Zynteglo may be considered **medically necessary** if the conditions indicated below are met.

Zynteglo may be considered **investigational** for all other indications.

Prior-Approval Requirements

Diagnosis

Patient must have the following:

Beta-thalassemia

AND ALL of the following:

a. Beta-thalassemia diagnosis has been confirmed by globin gene testing
b. Patient requires regular peripheral blood transfusions to maintain target hemoglobin levels
c. Patient has **ONE** of the following:
    i. Documented history of receiving transfusions of ≥100 mL per kilogram of body weight of packed red cells per year
    ii. Disease had been managed under standard thalassemia guidelines

with ≥8 transfusions per year in the previous 2 years

d. Age 16+ **only**: Karnofsky performance status of ≥80
(e.g., https://hemonc.org/wiki/Performance_status)
e. Age <16 **only**: Lansky performance status of ≥80
(e.g., https://hemonc.org/wiki/Performance_status)

AND NONE of the following:

a. Availability of human leukocyte antigen-identical or human leukocyte antigen-matched donor
b. Evidence of severe iron overload (e.g., T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec)
c. Advanced liver disease (e.g., evidence of cirrhosis, active hepatitis, LFTs > 3 times the upper limit of normal, etc.)
d. Baseline estimated glomerular filtration rate (eGFR) <70 mL/min/1.73 m^2
e. History of receiving prior gene therapy or allogenic hematopoietic stem cell transplant
f. Any prior or current malignancy or myeloproliferative or significant immunodeficiency disorder
g. Any immediate family member (i.e., parents or siblings) with a known Familial Cancer Syndrome
h. Active uncontrolled HCV, HIV, or HBV infection
i. Contraindication to the use of G-CSF, plerixafor, busulfan, or any other medicinal products required during myeloablative conditioning
j. White blood cell count <3 x 10^9/L and/or platelet count <100 x 10^9/L not related to hypersplenism

Prior – Approval *Renewal* Requirements

None

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity One infusion (only one PA approval for one infusion per lifetime)

Prior – Approval *Renewal* Limits

None

Rationale

Summary

Zynteglo is an autologous hematopoietic stem cell-based gene therapy. It is for one-time single-dose intravenous use only and is indicated for the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions. Patients are required to undergo HSC mobilization following apheresis to obtain CD34+ cells for Zynteglo manufacturing. Full myeloablative conditioning must be administered before infusion of Zynteglo (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Zynteglo while maintaining optimal therapeutic outcomes.

References

1. Zynteglo [package insert]. Somerville, MA: Bluebird Bio, Inc.; August 2022.

Policy History

Date	Action/Reason
September 2022	Addition to PA
October 2022	Per FEP: revised wording of leukocyte donor criterion to “Availability of human leukocyte antigen-identical or human leukocyte antigen-matched donor”
December 2022	Annual review
December 2023	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 8, 2023 and is effective on January 1, 2024.