DR.022.B Zynteglo™ (betibeglogene autotemcel)

Original Implementation Date : 08/21/2024
Version [B] Date : 08/21/2025
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Last Reviewed Date: 08/19/2026

Thank you for being a valued provider for members in one or more of our health plans: Jefferson Health Plans Medicare Advantage, Jefferson Health Plans Individual and Family Plans, Jefferson Health Plans CHIP, and/or Jefferson Health Plans EverWell (our Medicaid plan).

PRODUCT VARIATIONS

This policy applies to all Jefferson Health Plans lines of business unless noted below.

Gene therapy is a benefit exclusion for Individual and Family (ACA) product lines and therefore, non-covered.

POLICY STATEMENT

The plan considers Zynteglo™ (betibeglogene autotemcel) medically necessary for its FDA approved indications when the prior authorization listed in this policy are met.

FDA APPROVED INDICATIONS

Gene Therapy is the introduction, removal, or change in the content of a person's genetic code with the goal of treating or curing a disease. It includes therapies such as gene transfer, gene modified cell therapy, and gene editing.

Zynteglo™ (betibeglogene autotemcel) is an autologous hematopoietic stem cell-based gene therapy indicated for the treatment of adult and pediatric patients with ß-thalassemia who require regular red blood cell (RBC) transfusions.

OFF-LABEL USE

N/A

PRIOR AUTHORIZATION CRITERIA

Prior authorization is required for Zynteglo™ (betibeglogene autotemcel). Requests for prior authorization of Zynteglo™ (betibeglogene autotemcel) will be approved for 18 months for 1 infusion.

Zynteglo™ (betibeglogene autotemcel) may be considered medically necessary when **ALL** of the following apply:

1. Is prescribed for an indication that is included in the U.S. Food and Drug Administration (FDA)-approved package labeling; **AND**

2. Is age-appropriate according to FDA-approved package labeling; **AND**

3. The dose and the number of treatments are consistent with FDA-approved package labeling; **AND**

4. Is prescribed by a specialist at a qualified treatment center for Zynteglo™ (betibeglogene autotemcel); **AND**

5. The member does not have a contraindication to the prescribed medication; **AND**

6. The member is not a prior recipient of gene therapy or an allogeneic hematopoietic stem cell transplant; **AND**

7. For treatment of transfusion-dependent ß-thalassemia, **both** of the following apply:

    a. Has genetic testing confirming diagnosis of ß-thalassemia.
    b. Has a history of at least 100 mL/kg/year or 8 transfusion episodes/year of packed red blood cell transfusions in the prior 2 years.

NOTE: If the beneficiary does not meet the clinical review guidelines listed above but, in the professional judgement of the physician reviewer, the

services are medically necessary to meet the medical needs of the beneficiary, the request for prior authorization will be approved.

DOSAGE AND ADMINISTRATION

See package labeling.

RISK FACTORS/SIDE EFFECTS

See package labeling.

MONITORING

See package labeling.

CLINICAL EVIDENCE

The efficacy of Zynteglo™ was evaluated in 2 ongoing Phase 3 open-label, single-arm, 24-month, multicenter studies in 41 patients aged 4 to 34 years with ß-thalassemia requiring regular transfusions. All patients were administered Zynteglo™ with a median (min, max) dose of 9.4 (5.0, 42.1) × 10^6 CD34+ cells/kg as an intravenous infusion.

Study 1 included 23 patients with ß-thalassemia. Efficacy was established based on achievment of tranfusion independence (TI). Defnined as a weighted average Hb ≥ 9 g/dL without any pRBC transfusions for a continuous period of ≥ 12 months at anytime during the study, after the infusion. Of 22 patients evaluable for TI, 20 (91%, 95% CI: 71, 99) achieved TI with a median (min, max) weighted average Hb during TI of 11.8 (9.7, 13.0) g/dL. All patients who achieved TI maintained TI, with a min, max duration of ongoing TI of 15.7+, 39.4+ months.

Study 2 included 18 patients with ß-thalassemia. Efficacy was established the same as Study 1. Of 14 patients evaluabel for TI, 12 (86%, 95% CI: 57, 98) achieved TI with a median (min, max) weighted average Hb during TI of 10.20 (9.3, 13.7) g/dL. All patients who achieved TI maintained TI, with a min, max duration of ongoing TI of 12.5+, 32.8+ months.

BACKGROUND

Thalassemia is an inherited blood disorder characterized by decreased hemoglobin production. There are two main types: α-thalassaemia and ß-thalassaemia. α-

thalassaemia occurs if genes related to α-globin protein are altered or missing and ß-thalassaemia is similar as it occurs when the ß-globin protein is affected. With these two types there are three major subtypes: thalassemia major, intermedia and minor.

Both the α-globin and ß-globin link with eachother to form adult hemoglobin and form a minor fraction of adult hemoglobin which forms fetal hemoglobin. If production of either globins decreases there will be unpaired globin chains which will cause them to accumulate within the developing red cell. If α-globin are not being produced there will be excess ß-globin chains (α-thalassaemia) and when ß-globin chains are not produced there is an excess of α-globin chains (ß-thalassaemia). When these excess chains accumulate in the red cells it results in destruction and reduces the availablility of hemoglobin to carry oxygen, referred to as anemia. To correct this a blood transfusion is usually required. Transfusion-dependent ß-thalassemia is the most severe form of ß-thalassemia. In this case the anemia must be corrected with regular blood transfusions or else the patient will die early in life.

Zynteglo™ is a $ß^{A-T87Q}$-globin gene therapy consisting of autologous CD34+ cells, containing hematopoietic stem cells (HSCs), transduced with BB305 LVV encoding $ß^{A-T87Q}$-globin, suspended in cryopreservation solution. It is intended for one-time administration to add functional copies of a modified form of the ß-globin gene ($ß^{A-T87Q}$-globin gene) into the patient's own HSCs and is prepared from the patient's own HSCs. After infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce RBCs containing biologically active $ß^{A-T87Q}$-globin that will combine with α-globin to produce functional adult Hb containing $ß^{A-T87Q}$-globin (HbA^{T87Q}). $ß^{A-T87Q}$-globin can be quantified relative to other globin species in peripheral blood using high-performance liquid chromatography. $ß^{A-T87Q}$-globin expression is designed to correct the ß/α-globin imbalance in erythroid cells of patients with ß-thalassemia and has the potential to increase functional adult HbA and total Hb to normal levels and eliminate dependence on regular pRBC transfusions.

CODING

Note: *The Current Procedural Terminology (CPT®), Healthcare Common Procedure Coding System (HCPCS), and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes that may be listed in this policy are for reference purposes only. Listing of a code in this policy does not imply that the service is covered and is not a guarantee of payment. Other policies and coverage guidelines may apply. When reporting services, providers/facilities should code to the highest level of specificity using the code that was in effect on the date the service was rendered. This list may not be all inclusive.*

CPT® is a registered trademark of the American Medical Association.

CPT Code	Description
N/A	N/A

HCPCS Code	Description
J3393	Injection, betibeglogene autotemcel, per treatment

ICD-10 Codes	Description
D56.1	Beta Thalassemia

DISCLAIMER

Approval or denial of payment does not constitute medical advice and is neither intended to guide nor influence medical decision making. Policy Bulletins are developed to assist in administering plan benefits and constitute neither offers of coverage nor medical advice. This Policy Bulletin may be updated and therefore is subject to change.

For Jefferson Health Plans Everwell and Jefferson Health Plans Chip products: Any requests for services that do not meet criteria set in PARP will be evaluated on a case-by-case basis.

POLICY HISTORY

This section provides a high-level summary of changes to the policy since the previous version.

Summary	Version	Version Date
2026 Annual Review. Revisions to Dosage & Administration, Risk Factors/Side Effects and Monitoring Sections. References updated.	B	08/21/2025

2025 Annual review. HCPCS and ICD 10 codes added. References updated.	B	08/21/2025
New policy.	A	8/21/2024

REFERENCES

1. Zynteglo™ [prescribing information]. Somerville, MA: bluebird bio, Inc.; August 2022.

2. Cappellini MD, Farmakis D, Porter J, Taher A, eds. 2021 Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT). 4th ed. Thalassaemia International Federation (TIF). Available at: https://thalassaemia.org.cy/. Accessed March 2024.

3. Emanuele Angelucci, MD,Edward J Benz, Jr, MD Hematopoietic stem cell transplantation and other curative therapies for transfusion-dependent thalassemia. UpToDate-literature review last updated: **Jun 12, 2026.**

4. Lai, X., Liu, L., Zhang, Z. et al. Hepatic veno-occlusive disease/sinusoidal obstruction syndrome after hematopoietic stem cell transplantation for thalassemia major: incidence, management, and outcome. Bone Marrow Transplant 56, 1635–1641 (2021).