Jefferson Health Plans

DR.022.A Zynteglo™ (betibeglogene autotemcel)

Original Implementation Date : 8/21/2024
Version [A] Date : 8/21/2024
Last Reviewed Date: 8/21/2024

PRODUCT VARIATIONS

This policy applies to all Jefferson Health Plans Medicaid, CHIP and Medicare product lines.

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

POLICY STATEMENT

Jefferson Health Plans 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 β-thalassemia who require regular red blood cell (RBC) transfusions.

OFF-LABEL USE

N/A

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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 Zynteglo™ (betibeglogene autotemcel) 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. Is prescribed a dose and number of treatments that are consistent with FDA-approved package labeling; **AND**

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

5. Does not have a contraindication to the prescribed medication; **AND**

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

7. For treatment of transfusion-dependent β-thalassemia, both of the following:

    a. Has genetic testing confirming diagnosis of β-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.

DOSAGE AND ADMINISTRATION

Zynteglo™ is a cell suspension for intravenous infusion. A single dose of Zynteglo™ contains a minimum of 5.0×10^6 CD34+ cells/kg of body weight, in one or more infusion bags.

Administration:

- For intravenous use only.
- Full myeloablative conditioning must be administered before infusion.
- Prophylaxis for hepatic veno-occlusive disease (VOD) is recommended.
- Prophylaxis for seizures should be considered.
- Do not use an in-line blood filter or an infusion pump.

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- Administer each infusion bag of Zynteglo™ via intravenous infusion over a period of less than 30 minutes.

Dose:

- Based on the number of CD34+ cells in the infusion bag(s) per kg of body weight.
- The minimum recommended dose is 5.0×10^6 CD34+ cells/kg.

RISK FACTORS/SIDE EFFECTS

The most common non-laboratory adverse reactions (incidence ≥ 20%) were mucositis, febrile neutropenia, vomiting, pyrexia (fever), alopecia (hair loss), epistaxis (nose bleed), abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus.

The most common Grade 3 or 4 laboratory abnormalities (> 50%) include neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia

Drug Interactions:

- *Anti-retrovirals and Hydroxyurea:* Do not take anti-retroviral medications or hydroxyurea for one month prior to mobilization, or for the expected duration for elimination of the medications, and until all cycles of apheresis are completed

- *Iron Chelation:* Discontinue iron chelators 7 days prior to initiation of myeloablative conditioning. Avoid use of myelosuppressive iron chelators for 6 months after infusion.

MONITORING

1. **Delayed Platelet Engraftment**: Monitor platelet counts until platelet engraftment and recovery are achieved. Patients should be monitored for thrombocytopenia and bleeding.

2. **Risk of Neutrophil Engraftment Failure**: Monitor absolute neutrophil counts (ANC) after infusion. If neutrophil engraftment does not occur administer rescue cells.

3. **Risk of Insertional Oncogenesis**: Monitor patients at least annually for hematologic malignancies for at least 15 years after infusion

4. **Hypersensitivity Reactions**: Monitor for hypersensitivity reactions during infusion.

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

Both the α-globin and β-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 β-globin chains (α-thalassaemia) and when β-globin chains are not produced there is an excess of α-globin chains (β-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 β-thalassemia is the most severe form of β-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 $\beta^{A\text{-}T87Q}$-globin gene therapy consisting of autologous CD34+ cells, containing hematopoietic stem cells (HSCs), transduced with BB305 LVV encoding $\beta^{A\text{-}T87Q}$-globin, suspended in cryopreservation solution. It is intended for one-time administration to add functional copies of a modified form of the β-globin gene ($\beta^{A\text{-}T87Q}$-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 $\beta^{A\text{-}T87Q}$-globin that will combine with α-globin to produce functional adult Hb containing $\beta^{A\text{-}T87Q}$-globin (HbA^{T87Q}). $\beta^{A\text{-}T87Q}$-globin can be

quantified relative to other globin species in peripheral blood using high-performance liquid chromatography. $\beta^{A\text{-}T87Q}$-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 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
J3590	Unclassified Biologics

ICD-10 Codes	Description
N/A	N/A

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 by Jefferson Health Plans 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.

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For HealthChoices (Medicaid) and Children's Health Insurance Program (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
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. Connor RF, Fosmarin AG, Tirnauer JS. What's new in hematology. UpToDate [internet database]. Waltham, MA: UpToDate Inc. Updated February 29, 2024. Accessed March 18, 2024.

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).