# betibeglogene autotemcel (Zynteglo®)

**Medicare Advantage Medical Policy # 094**
Original Effective Date: 05/01/2025
Current Effective Date: 05/01/2025

*Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

# When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider betibeglogene autotemcel (Zynteglo®)‡ for the treatment of β-thalassemia to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of betibeglogene autotemcel (Zynteglo) will be considered when all of the following criteria are met:

- Patient has a documented diagnosis of β-thalassemia by globin gene testing; AND
- Patient requires regular peripheral blood transfusions to maintain target hemoglobin levels; AND
- Patient has ONE of the following:
  - Documented history of receiving transfusions of ≥100 mL per kg of body weight of packed red cells per year; OR
  - Disease managed under standard thalassemia guidelines with ≥8 transfusions per year in the previous 2 years at the time of treatment decision; AND
- Karnofsky performance status of ≥80 for patients ≥16 years of age or a Lansky performance status of ≥80 for patients <16 years of age; AND
- Patient has a negative serologic test for HIV infection; AND
- Patient does NOT have:
  - Availability of human leukocyte antigen-identical or human leukocyte antigen-matched donor; OR
  - T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec or other evidence of severe iron overload in the opinion of treating physician; OR
  - Advanced liver disease as evidenced by at least ONE of the following:
    - Persistent aspartate transaminase, alanine transaminase, or direct bilirubin value greater than 3 times the upper limit of normal; OR
    - Baseline prothrombin time or partial thromboplastin time greater than 1.5 times the upper limit of normal; OR
    - Magnetic resonance imaging of the liver demonstrating clear evidence of cirrhosis; OR

        - Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis; OR
    - Baseline estimated glomerular filtration rate less than 70 mL/min/1.73 $m^2$; OR
    - History of receiving prior gene therapy or allogenic hematopoietic stem cell transplant; OR
    - Any prior or current malignancy (with the exception of adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin) or myeloproliferative or significant immunodeficiency disorder; OR
    - Any immediate family member (i.e., parent or siblings) with a known Familial Cancer Syndrome (including but not limited to hereditary breast and ovarian cancer syndrome, hereditary nonpolyposis colorectal cancer syndrome, and familial adenomatous polyposis); OR
    - Active, uncontrolled HCV or HBV infection; OR
    - Contraindication to the use of granulocyte colony stimulating factor (G-CSF), plerixafor, busulfan, or any other medicinal products required during myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients; OR
    - A white blood cell count less than 3 x $10^9$/L and/or platelet count less than 100 x $10^9$/L not related to hypersplenism

# When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of betibeglogene autotemcel (Zynteglo) when the following criteria are not met to be **not medically necessary.****

- Karnofsky performance status of $\geq$80 for patients $\geq$16 years of age or a Lansky performance status of $\geq$80 for patients <16 years of age; AND
- Patient does NOT have:
    - Availability of human leukocyte antigen-identical or human leukocyte antigen-matched donor; OR
    - T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec or other evidence of severe iron overload in the opinion of treating physician; OR
    - History of receiving prior gene therapy or allogenic hematopoietic stem cell transplant; OR
    - Any prior or current malignancy (with the exception of adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin) or myeloproliferative or significant immunodeficiency disorder; OR
    - Any immediate family member (i.e., parent or siblings) with a known Familial Cancer Syndrome (including but not limited to hereditary breast and ovarian cancer

syndrome, hereditary nonpolyposis colorectal cancer syndrome, and familial adenomatous polyposis); OR
- Active, uncontrolled HCV or HBV infection; OR
- Contraindication to the use of granulocyte colony stimulating factor (G-CSF), plerixafor, busulfan, or any other medicinal products required during myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients; OR
- A white blood cell count less than 3 x $10^9$/L and/or platelet count less than 100 x $10^9$/L not related to hypersplenism

# When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Health Plan considers the use of betibeglogene autotemcel (Zynteglo) for any indication other than transfusion dependent β-thalassemia or when the patient selection criteria are not met (except those noted to be **not medically necessary****) to be **investigational.*** Additionally, the Health Plan considers repeat treatment with betibeglogene autotemcel (Zynteglo) to be **investigational.***

# Background/Overview

Zynteglo is a gene therapy indicated for the treatment of adult and pediatric patients with transfusion-dependent β-thalassemia. It works by adding functional copies of a modified form of the beta-globin gene into a patient's own hematopoietic stem cells to enable the production of a modified functional adult hemoglobin. Once a patient has this modified beta-globin gene, they have the potential to increase Zynteglo-derived adult hemoglobin and total hemoglobin to normal or near normal levels, which can eliminate the need for regular transfusions of red blood cells (RBCs). Full myeloablative conditioning must be administered before infusion of Zynteglo. The administration and preparation processes are complex and require hospitalization. The main steps involved include:

- HSC mobilization and apheresis (occurs 70-90 days before infusion of drug product)
- Myeloablative conditioning
- Drug product intravenous infusion
- Hospitalization for 3-6 weeks after infusion

Additionally, it is recommended that patients receive prophylaxis for hepatic veno-occlusive disease and seizures. Monitoring of platelet counts and absolute neutrophil counts should be continued to ensure platelet engraftment and neutrophil engraftment are achieved. Patients should also be monitored at least annually for hematologic malignancies for at least 15 years following Zynteglo infusion. Iron chelators should be discontinued at least 7 days prior to initiation of conditioning and

avoided for 6 months following Zynteglo infusion. Of note, patients with human immunodeficiency virus (HIV) infection are not eligible to receive Zynteglo as the prescribing label states that apheresis material from individuals with a positive test for HIV will not be accepted for Zynteglo manufacturing.

β-thalassemia is an inherited blood disorder caused by a mutation of the hemoglobin beta (*HBB*) gene responsible for making the beta-globin protein. When this protein is absent, the disease is referred to as beta-zero ($\beta^0$) thalassemia. Whereas if the protein is simply reduced in function, the disease is referred to as beta-plus ($\beta^+$) thalassemia. The condition can be further classified by severity. β-thalassemia major is associated with severe symptoms of anemia diagnosed in childhood while patients with β-thalassemia minor may be asymptomatic or exhibit minor anemia. Thalassemia intermedia has a variable severity with a broad range of symptoms between the minor and major forms. Recently, patients have been classified according to their transfusion status (i.e., transfusion-dependent β-thalassemia or non-transfusion-dependent β-thalassemia.) Clinical studies typically define "transfusion dependence" as a history of at least 100 mL/kg/year of peripheral red blood cells or ≥8 transfusions of peripheral red blood cells per year for the prior 2 years. Symptoms of β-thalassemia include shortness of breath, fatigue, weakness, dizziness, jaundice, and/or headaches. Failure to thrive is observed in affected infants. If untreated, bone deformities may develop and overall disease complications lead to a short life span. Even with treatment, severe complications may arise due to iron overload secondary to increased intestinal absorption and frequent blood transfusions.

The main treatment option available for transfusion dependent β-thalassemia is blood transfusion to improve anemia and suppress ineffective erythropoiesis. Transfusions also prevent the majority of skeletal and neurological complications of the disease but are associated with severe complications such as alloimmunization, transmission of infectious disease, and iron overload. Typically, blood transfusions are initiated based on inability of the patient to compensate for low hemoglobin, increases in symptoms for ineffective erythropoiesis, or initial hemoglobin levels <6 g/dL. Transfusions are usually given once every 3-4 weeks and the amount of blood transfused varies based on the pretransfusion hemoglobin levels (typical target is 9-10 g/dL). Additional treatments for this condition include chelation therapy for patients with iron overload, splenectomy when hypersplenism increases transfusion requirements, hydroxyurea, luspatercept-aamt (Reblozyl®)‡ to decrease transfusion burden, and allogeneic hematopoietic cell transplant (HCT) for patients with an HLA-matched sibling donor for whom benefit outweighs the risks. Although allogeneic HCT is considered curative, only approximately 25% of patients have a matched sibling donor and the likelihood of success decreases with patient age. Zynteglo provides a curative treatment option for patients who may not be candidates for HCT based on lack of a suitable donor.

# FDA or Other Governmental Regulatory Approval

**U.S. Food and Drug Administration (FDA)**

Zynteglo was approved in August 2022 for the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions.

# Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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. Following completion of the 24-month parent studies, patients were invited to enroll in an ongoing long-term safety and efficacy follow-up study for an additional 13 years.

Patients were considered to be eligible for the Phase 3 studies if they had a history of transfusions of at least 100 mL/kg/year of packed red blood cells (pRBCs) or with 8 or more transfusions of pRBCs per year in the 2 years preceding enrollment. Patients who had severely elevated iron in the heart (i.e., patients with cardiac T2* less than 10 msec by MRI) or advanced liver disease were not accepted into the studies. MRI of the liver was performed on all patients. Patients older than 18 years with MRI results demonstrating liver iron content $\geq$15 mg/g were excluded from the studies unless a liver biopsy could provide additional data to confirm eligibility. Patients with a liver biopsy demonstrating bridging fibrosis, cirrhosis, or active hepatitis, were also excluded.

All patients were administered G-CSF and plerixafor to mobilize stem cells prior to the apheresis procedure. Apheresis generally occurred on mobilization Day 5 and 6 and if a third day of collection was needed, plerixafor and G-CSF dosing was extended to Day 6. Most patients collected the minimum number of CD34+ cells to manufacture Zynteglo with 1 cycle of mobilization and apheresis.

All patients received full myeloablative conditioning with busulfan prior to treatment with Zynteglo. After completion of the 4-day course of busulfan, a washout period of at least 48 hours was required before Zynteglo administration. Busulfan levels were measured 48 hours after final dose of busulfan for retrospective confirmation of adequate washout. All patients received anti-seizure prophylaxis with agents other than phenytoin prior to initiating busulfan. Prophylaxis for hepatic veno-occlusive disease/hepatic sinusoidal obstruction syndrome was required with ursodeoxycholic acid or defibrotide per institutional guidelines.

All patients (n=41) were administered Zynteglo with a median (min, max) dose of 9.4 (5.0,42.1)x$10^6$ CD34+ cells/kg as an intravenous infusion. G-CSF was not recommended for 21 days after Zynteglo infusion in phase 3 studies. A total of 24% of patients (n=10/41) received G-CSF within 21 days after Zynteglo infusion. Neutrophil engraftment was reported on median (min, max) Day 26 (13, 39) after Zynteglo infusion.

In Study 1, 23 patients with β-thalassemia requiring regular transfusions and with a non-$\beta^0/\beta^0$ genotype received Zynteglo with a median duration of follow up of 29.5 months. All patients remain alive at last follow-up and there were no cases of graft versus-host disease (GVHD), graft failure, or graft rejection. The benefit of Zynteglo was established based on achievement of transfusion independence (TI), defined as a weighted average Hb $\geq$9 g/dL without any pRBC transfusions for a continuous period of $\geq$12 months at any time during the study, after infusion of Zynteglo. Of 22 patients evaluated 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) g/dL. All patients who achieved TI maintained TI, with a min, max duration of ongoing TI of 15.7+, 39.4+ months. The median (min, max) time to last pRBC transfusion prior to TI was 0.9 (0.5, 2.4) months following Zynteglo infusion. For the patients who were evaluable for TI and did not achieve TI (n=2), a reduction of 32% and 31% in transfusion volume requirements and a reduction of 30% and 26% in transfusion frequency were observed from 6 months post-drug product infusion to last follow-up compared to pre-enrollment requirements.

In Study 2, 18 patients with β-thalassemia requiring regular transfusions and a $\beta^0/\beta^0$ or non $\beta^0/\beta^0$ genotype received Zynteglo with a median (min, max) duration of follow-up of 24.6 (4.1, 35.5) months. All patients remain alive at last follow-up with no cases of GVHD, graft failure, or graft rejection. The efficacy of Zynteglo was established based on achievement of TI which was defined as a weighted average Hb $\geq$9 g/dL without any pRBC transfusions for a continuous period of $\geq$12 months at any time during the study, after infusion of Zynteglo. Of the 14 patients evaluable for TI, 12 (86%, 95% CI: 57, 98) achieved TI with a median (min, max) weighted average Hb during TI of 10.2 (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 (n=12). The median (min, max) time to last pRBC transfusion prior to TI was 0.8 (0, 1.9) months following Zynteglo. For the patients who were evaluable for TI and did not achieve TI (n=2), a reduction of 92% and 3% in transfusion volume requirements and a reduction of 87% and 21% in transfusion frequency were observed from 6 months post-drug product infusion to last follow-up compared to pre-enrollment requirements.

# References

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# Policy History

Original Effective Date: 05/01/2025
Current Effective Date: 05/01/2025
02/18/2025 UM Committee review. New policy.
Next Scheduled Review Date: 02/2026

# Coding

*The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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*contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*



Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type | Code |
|---|---|
| CPT | No codes |
| HCPCS | J3393 |
| ICD-10 Diagnosis | All related diagnoses |

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services

at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

**NOTICE:** Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

## Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.