09-J4000-35

Original Effective Date: 11/15/22

Reviewed: 01/08/25

Revised: 02/15/25

Subject: Betibeglogene Autotemcel (Zynteglo®) IV Infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Betibeglogene autotemcel (Zynteglo) is an intravenous (IV) autologous hematopoietic stem cell-based gene therapy approved by the U.S. Food and Drug Administration (FDA) in August 2022 for the treatment of adult and pediatric patients with beta (β)-thalassemia who require regular red blood cell (RBC) transfusions. Betibeglogene autotemcel (beti-cel) is the first gene-therapy to be approved for the treatment of β-thalassemia. Beti-cel was previously granted orphan drug designation by the FDA for the treatment of β -thalassemia major and intermedia in 2013. Beti-cel works by adding functional copies of a modified β-globin gene into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with a lentiviral vector (LVV). After infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce RBCs containing biologically active βA-T87Q-globin (a modified β-globin protein) that will combine with α-globin to produce functional adult Hb containing βA-T87Q-globin (HbAT87Q). βA-T87Q-globin expression is designed to correct the β/α-globin imbalance in erythroid cells and increase functional adult HbA and total Hb to normal levels and eliminate dependence on regular RBC transfusions.

Beta thalassemia is a rare, inherited disorder characterized by gene mutations resulting in absent (beta zero, B^0) or reduced (beta plus, B^+) production of the β-globin chains in hemoglobin. The reduced synthesis of β-globin leads to an imbalance in the alpha/beta-globin chain ratio and the excess of unpaired alpha-globin chains leads to premature death of RBCs and their precursors in the bone marrow. Ineffective erythropoiesis leads to anemia and various subsequent complications including hemolysis, hypercoagulability, iron overload secondary to frequent RBC transfusions, heart disease, and hepatic cirrhosis. Over 200 different mutations that affect the β-globin gene, most often point mutations, have been described in patients with beta thalassemia. Patient genotypes may be either homozygous (e.g., B^+/B^+, B^0/B^0) or compound heterozygous (e.g., B^0/B^+). Persons with only one defective

β-globin gene (e.g., B/B^{+}, B/B^{0}) are typically asymptomatic and are known as β-thalassemia carriers (also called thalassemia minor, beta thalassemia trait, and heterozygous beta thalassemia). Phenotypic findings range widely in non-carrier patients and are often categorized as thalassemia major (lack of or very minimal β-globin production; a.k.a., Cooley's anemia and Mediterranean anemia) or thalassemia intermedia (some residual β-globin production). Individuals with thalassemia major become severely symptomatic in the first two years of life and require regular RBC transfusions to survive. It is estimate that approximately 1,300 people in the U.S. currently live with transfusion-dependent (TD) β-thalassemia. Thalassemia intermedia includes patients who present later and often do not require regular transfusion; however, transfusion needs are highly variable in this group. There are also β-thalassemias associated with other Hb anomalies, such as β-thalassemia and hemoglobin E (HbE) (e.g., B^{E}/B^{+}, B^{E}/B^{0}). Diagnosis of β-thalassemia is based on an assessment of various clinical signs and symptoms. Typical laboratory tests include a complete blood count (CBC), peripheral blood smear, iron studies, and qualitative and quantitative hemoglobin analysis (typically by electrophoresis or chromatography). In patients with β-thalassemia major or intermedia, hemoglobin analysis will find low levels of adult hemoglobin (HbA) and high level of fetal hemoglobin (HbF). Molecular genetic testing can also be done to determine the exact genotype of the patient. Current treatment options for TB β-thalassemia are extremely limited. Packed red blood cell (pRBC) and iron chelation therapy (ICT) are the mainstays of treatment. Prior to beti-cel, the only potentially curative treatment was allogeneic hematopoietic stem cell transplantation (HSCT) which is typically limited to young patients with well-matched donors and also requires long-term immunosuppression to prevent or treat transplant related immunological complications such as graft-vs-host disease (GvHD) and rejection. Overall thalassemia-free survival with HSCT is >85% in children and 65% in adults. Only about 25% of TD β-thalassemia patients have a matched sibling donor.

The safety and efficacy of beti-cel leading to FDA approval was based on two 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 (Study 1 and 2 per the product labeling). 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 (Study 3 per the product labeling). Patients were considered to be eligible for the Phase 3 studies if they ≤50 years of age, had a history of transfusions of at least 100 mL/kg/year of pRBC or with 8 or more transfusions of pRBCs per year in the 2 years preceding enrollment, and were clinically stable and eligible to undergo HSCT. Patients with a known and available HLA-matched family donor were excluded. Patients who had severely elevated iron in the heart (i.e., patients with cardiac T2* less than 10 msec by magnetic resonance imaging [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 ≥15 mg/g underwent liver biopsy for further evaluation. Patients younger than 18 years with MRI results demonstrating liver iron content ≥15 mg/g were excluded from the studies unless a liver biopsy (at the discretion of the investigator) 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. All patients received full myeloablative conditioning with busulfan prior to treatment with beti-cel. After completion of the 4-day course of busulfan, a washout period of at least 48 hours was required before beti-cell administration. All patients received anti-seizure prophylaxis with agents other than phenytoin prior to initiating busulfan. Prophylaxis for hepatic veno-occlusive disease

(VOD)/hepatic sinusoidal obstruction syndrome was required with ursodeoxycholic acid or defibrotide, per institutional guidelines. All patients were administered beti-cel with a median (min, max) dose of 9.4 (5.0, 42.1) x 10^6 CD34+ cells/kg as an IV infusion. Neutrophil engraftment was reported on median (min, max) Day 26 (13, 39) after beti-cel infusion. Since beti-cel is an autologous therapy, long-term immunosuppressive agents were not required.

Study 1 [HGB-207 (Northstar-2), NCT02906202] included 23 patients with β-thalassemia requiring regular transfusions and with a non-β0/β0 genotype. The median (min, max) age was 15 (4, 34) years, 52% were females, 57% were Asian, and 35% were White. Baseline transfusion volume was a median (min, max) of 208 (142, 274) mL/kg/year and the baseline transfusion frequency was a median (min, max) of 16 (12, 37) transfusion per year. Nineteen out of 23 patients have rolled over into a long-term follow-up study [Study 3 (LFT-303), NCT02633943] after Month 24. The median (min, max) duration of follow-up is 29.5 (13.0, 48.2) months. All patients remained alive at last follow-up. There were no cases of graft versus-host disease (GVHD), graft failure, or graft rejection in the clinical studies. The benefit of beti-cel was established based on achievement of transfusion independence (TI), defined as a weighted average Hb ≥9 g/dL without any pRBC transfusions for a continuous period of ≥12 months at any time during the study, after infusion of beti-cel. 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. The median (min, max) time to last pRBC transfusion prior to TI was 0.9 (0.5, 2.4) months following beti-cel 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. After beti-cel infusion, patient iron removal therapy was managed at physician discretion. Thirteen of the 20 patients who achieved TI were not on chelation therapy as of last follow-up. Of these, 9 (9/13 = 69%) patients did not restart chelation. Four patients (4/13 = 31%) restarted and then stopped iron chelation with a median time from last iron chelation use to last follow-up of 22.7 (7.1, 23.4) months. Of the 20 patients who achieved TI, 7 patients (35%) received phlebotomy to remove iron.

Study 2 [HGB-212 (Northstar-3, NCT03207009] included 18 patients with β-thalassemia requiring regular transfusions and a β0/β0 or non-β0/β0 (IVS-I-110/IVS-I-110 or IVS-I-110/ β0) genotype. The median (min, max) age was 13 (4, 33) years, 44% were females, 39% were Asian, and 56% were White. Baseline transfusion volume was a median (min, max) of 194 (75, 289) mL/kg/year and the baseline transfusion frequency was a median (min, max) of 17 (11, 49) transfusion per year. Ten out of 18 patients have rolled over into the long-term follow-up study (Study 3) after Month 24. The median (min, max) duration of follow-up is 24.6 (4.1, 35.5) months. All patients remained alive at last follow-up. There were no cases of GVHD, graft failure, or graft rejection in the clinical study. The efficacy of beti-cel was based on achievement of TI using the same criteria as Study 1. Fourteen patients are evaluable for TI. Of these, 12/14 (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. The median (min, max) time to last pRBC transfusion prior to TI was 0.8 (0.0, 1.9) months following beti-cell infusion. 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. After beti-cel infusion, patient iron removal therapy was

managed at physician discretion. Seven of the 12 patients who achieved TI were not on chelation therapy as of last follow-up. Of these, three (3/7 = 43%) patients did not restart chelation. Four patients (4/7 = 57%) restarted and then stopped iron chelation with a median time from last iron chelation use to last follow-up of 7.2 (6.0, 21.4) months. Of the 12 patients who achieved TI, one (8%) received phlebotomy to remove iron. All 32 patients in the Phase 3 studies who achieved TI with beti-cell maintained TI. These patients exhibited durable normal or near-normal total hemoglobin levels with a median (min, max) unsupported total Hb of 11.4 (9.5, 14.8) g/dL at last follow-up.

POSITION STATEMENT:

The administration of betibeglogene autotemcel (Zynteglo) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "11"):

1. Member has a documented diagnosis of beta-thalassemia (may include hemoglobin E/beta thalassemia and beta-thalassemia with mutation and/or multiplication of alpha globin) as evidence by beta globin (HBB) gene analysis showing pathogenic variants on **BOTH** genes - laboratory or medical record documentation of the genetic testing results must be submitted
2. Member has transfusion-dependent disease defined by **EITHER** of following criteria ("a" or "b") – medical record documentation of the member's transfusion history from at least the past two years must be submitted
    a. History of receiving transfusions of ≥100 milliliter per kilogram of body weight per year (mL/kg/year) of packed red cells (pRBCs) in the prior two years
    b. History of receiving eight or more transfusions of pRBCs per year in the prior two years [only applicable for member 12 years of age or older]
3. Member is at least 4 years of age at the time of treatment
4. Member is clinically stable and able to undergo a hematopoietic stem cell transplant (HSCT) in the opinion of treating physician
5. Member has a negative serologic test for HIV infection (i.e., the member is **NOT** HIV positive)
6. Member does **NOT** have a willing, able, and suitable human leukocyte antigen (HLA)-matched family donor
7. Member will **NOT** use prophylactic HIV anti-retroviral medication or hydroxyurea within 30 days prior to stem cell mobilization and until all cycles of apheresis are completed
8. Member does **NOT** have **ANY** of the following ("a" to "g"):
    a. Baseline white blood cell count (WBC) less than 3 x 10^9/L and/or a baseline platelet count less than 100 x10^9/L not related to hypersplenism
    b. Severely elevated iron in the heart defined as a cardiac T2* less than 10 msec by magnetic resonance imaging (MRI) or other evidence of severe iron overload in the opinion of treating physician
    c. MRI of the liver with results demonstrating liver iron content ≥15 mg/g (unless biopsy confirms absence of advanced disease)
    d. Advanced liver disease defined as **ANY** of the following ("i" to "iv"):

i. Persistent aspartate transaminase (AST), alanine transaminase (ALT), or direct bilirubin value greater than 3-times the upper limit of normal (ULN)

ii. Baseline prothrombin time or partial thromboplastin time greater than 1.5-times the ULN

iii. MRI of the liver demonstrating clear evidence of cirrhosis

iv. Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis

e. Baseline estimated glomerular filtration rate (eGFR) less than 70 mL/min/1.73 m^2

f. 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)

g. Active infection, including uncontrolled HCV or HBV infection

9. Member has **NOT** previously received gene therapy (including betibeglogene autotemcel) **OR** an allogenic HSCT in their lifetime
10. Betibeglogene autotemcel will be administered at a Zynteglo Qualified Treatment Center (QTC)
11. The administration of betibeglogene autotemcel will not exceed one single dose as provided by the manufacturer

Approval duration: 12 months to allow for a one-time infusion of therapy

Betibeglogene autotemcel (Zynteglo) is considered **experimental or investigational** for all other thalassemias, hemoglobinopathies, or any other indications, including but not limited to the following, due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcome:

- Alpha thalassemia without concomitant beta thalassemia
- Sickle cell beta thalassemia [also known as hemoglobin S (HbS)-beta-thalassemia disease]

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- For the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions
    - Beti-cel is provided as a single dose for infusion containing a suspension of CD34+ cells in one or more infusion bags. The minimum recommended dose is 5.0×10^6 CD34+ cells/kg.
- Before mobilization, apheresis, and myeloablative conditioning are initiated, confirm that hematopoietic stem cell (HSC) transplantation is appropriate for the patient.
- It is recommended that patients be maintained at a hemoglobin (Hb) ≥ 11 g/dL for at least 30 days prior to mobilization and 30 days prior to myeloablative conditioning.

- Refer to the product labeling regarding the recommendations for mobilization, apheresis, myeloablative conditioning, receipt, and storage of beti-cel, preparation of the infusion, and administration.
- Standard procedures for patient management after HSC transplantation should be followed after beti-cel infusion.

Dose Adjustments

- Hepatic Impairment – Beti-cel has not been studied in patients with hepatic impairment. Patients should be assessed for hepatic impairment to ensure HSC transplantation is appropriate.
- Renal Impairment – Beti-cell has not been studied in patients with renal impairment. Patients should be assessed for renal impairment, defined as creatinine clearance ≤ 70 mL/min/1.73 m^2, to ensure HSC transplantation is appropriate.

Drug Availability

- Supplied in up to four infusion bags containing a frozen suspension of genetically modified autologous cells, enriched for CD34+ cells. Each bag contains approximately 20 mL. Each infusion bag is individually packed within an overwrap in a metal cassette. Zynteglo is shipped from the manufacturing facility to the treatment center storage facility in a cryoshipper, which may contain multiple metal cassettes intended for a single patient. A Lot Information Sheet is affixed inside the shipper.
    - 20 mL infusion bag, overwrap, and metal cassette: NDC 73554-3111-01.
- Match the identity of the patient with the patient identifiers on the metal cassette(s), infusion bag(s), and Lot Information Sheet upon receipt.
    - Keep the infusion bag(s) in the metal cassette(s) and store in the vapor phase of liquid nitrogen at less than or equal to -140°C (≤ -220°F) until ready for thaw and administration.
    - Thaw Zynteglo prior to infusion.
    - Do not re-freeze after thawing.
    - Do not irradiate Zynteglo, as this could lead to inactivation.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Delayed Platelet Engraftment**: Delayed platelet engraftment has been observed with beti-cel treatment. Bleeding risk is increased prior to platelet engraftment and may continue after engraftment in patients with prolonged thrombocytopenia; 15% of patients had ≥ Grade 3 decreased platelets on or after Day 100. Patients should be made aware of the risk of bleeding until platelet recovery has been achieved. Monitor patients for thrombocytopenia and bleeding according to standard guidelines. Conduct frequent platelet counts until platelet engraftment and platelet recovery are achieved. Perform blood cell count determination and other appropriate testing whenever clinical symptoms suggestive of bleeding arise.
- **Risk of Neutrophil Engraftment Failure**: There is a potential risk of neutrophil engraftment failure after treatment with beti-cel. Neutrophil engraftment failure is defined as failure to achieve three consecutive absolute neutrophil counts (ANC) ≥ 500 cells/microliter obtained on different days by Day 43 after infusion of beti-cel. Monitor neutrophil counts until engraftment has been achieved. If neutrophil engraftment failure occurs in a patient treated with beti-cel, provide rescue treatment with the back-up collection of CD34+ cells.
- **Risk of Insertional Oncogenesis:** There is a potential risk of lentiviral vector (LVV)-mediated insertional oncogenesis after treatment with beti-cel. Patients treated with beti-cel may develop hematologic malignancies and should be monitored lifelong. Monitor for hematologic malignancies with a complete blood count (with differential) at Month 6 and Month 12 and then at least annually for at least 15 years after treatment with beti-cel, and integration site analysis at Months 6, 12, and as warranted. In the event that a malignancy occurs, contact bluebird bio at 1-833-999-6378 for reporting and to obtain instructions on collection of samples for testing.
- **Hypersensitivity Reactions**: Allergic reactions may occur with the infusion of beti-cel. The dimethyl sulfoxide (DMSO) in beti-cel may cause hypersensitivity reactions, including anaphylaxis.
- **Anti-retroviral and Hydroxyurea Use:** Patients should not take prophylactic HIV anti-retroviral medications or hydroxyurea for at least one month prior to mobilization, or for the expected duration for elimination of the medications, and until all cycles of apheresis are completed. If a patient requires anti-retrovirals for HIV prophylaxis, then confirm a negative test for HIV before beginning mobilization and apheresis of CD34+ cells.
- **Interference with Serology Testing**: Patients who have received beti-cel are likely to test positive by polymerase chain reaction (PCR) assays for HIV due to integrated BB305 LVV proviral DNA, resulting in a false-positive test for HIV. Therefore, patients who have received beti-cel should not be screened for HIV infection using a PCR-based assay.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J3393	Injection, betibeglogene autotemcel, per treatment

ICD-10 Diagnosis Codes That Support Medical Necessity

D56.1	Beta thalassemia

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Gene Therapy - Gene therapies treat diseases by modifying or manipulating the expression of a gene or altering the properties of living cells for therapeutic use including: (1) replacing a disease-causing gene with a healthy copy of the gene, (2) inactivating a disease-causing gene that is not functioning properly, or (3) introducing a new or modified gene into the body to help treat a disease.

RELATED GUIDELINES:

Luspatercept-aamt (Reblozyl) Injection, 09-J3000-61

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 1/08/25.

GUIDELINE UPDATE INFORMATION:

11/15/22	New Medical Coverage Guideline.
01/01/23	Revision to guidelines consisting of updates to the position statement. Diagnostic criteria, donor requirements, exclusion criteria, and duration of approval were updated.
02/15/24	Review and revision to guidelines consisting of reference updates.
07/01/24	Revision: Added HCPCS code J3393 and deleted code J3590.
02/15/25	Review and revision to guidelines consisting of updating references.