Mass General Brigham
Health Plan

Zynteglo
(betibeglogene autotemcel)

Policy Number: 079

	Commercial and Qualified Health Plans	MassHealth	Medicare Advantage
Authorization required	X	X	X
Authorization not required			
Not Covered			

Overview

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.

Coverage Criteria

1. Criteria for Approval (The member must meet **all** of the following requirements):
    - The member has confirmed and symptomatic genetic diagnosis of transfusion dependent β-thalassemia with a non-β0/β0 or β0/β0 genotype.
    - The member is transfusion-dependent with a history of at least 100 mL/kg/year of packed red blood cells (pRBC) in the previous two years OR be managed under standard thalassemia guidelines with ≥ 8 transfusions of pRBCs per year in the previous two years.
    - The member is between 4 and 50 years of age at the time of treatment decision/consent, and meets both of the following criteria:
        a) Member weighs at least 6 kg; and
        b) Member is reasonably anticipated to provide at least the minimum number of cells required to initiate the manufacturing process
    - The member has not previously received Zynteglo.
    - Iron chelation therapy has been discontinued for at least 7 days prior to initiation of conditioning.
    - The prescribing physician is a hematologist who specializes in the treatment of Beta-Thalassemia.
    - The member will have treatment administered at a Zynteglo Qualified Treatment Center (Zynteglo QTC).
    - Documentation of ONE of the following:
        a) A recent (i.e. within 30 days) white blood cell count of at least 3 x 109/L;
        b) A recent (i.e. within 30 days) platelet count of at least 100 x 109/L.
    - Documentation of an estimated glomerular filtration rate (eGFR) of at least 70 mL/min/1.73 m^2
2. Dosing and Administration
    - The member will receive a single-dose Zynteglo intravenously infusion within accordance of the FDA approved labeling; 1.1 x 10^{14} vector genomes (vg) per kilogram of body weight.
3. Duration of Therapy
    - Single-dose one-time intravenous infusion per lifetime.
    - A single dose contains a minimum of 5.0 × 106 CD34+ cells/kg of body weight, in one or more infusion bags.

- Full myeloablative conditioning with busulfan must be administered before infusion of Zynteglo.
- The member should receive prophylaxis for hepatic veno-occlusive disease (VOD) / hepatic sinusoidal obstruction syndrome.
- The member should receive prophylaxis for seizures with agents other than phenytoin.

4. Facility Criteria
    - The medication is prescribed by a hematologist and/or a stem cell transplant specialist
    - The treatment will be administered at a Zynteglo Qualified Treatment Center

5. Exclusions
    - The member has HIV-1 or HIV-2 infection.
    - The member has a prior or current malignancy, a significant immunodeficiency, or myeloproliferative disorder (with the exception of adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin).
    - The member does not have a parent or sibling with a known Familial Cancer Syndrome (included but not limited to hereditary breast and ovarian cancer syndrome, hereditary non-polyposis colorectal cancer syndrome, and familial adenomatous polyposis) or the member has not been shown to carry the abnormal gene for Familial Cancer Syndrome.
    - The member does not have active bacterial, viral, fungal, parasitic infection such as HIV-1 or HIV-2 infection. Those with antibody evidence of hepatitis B infection are eligible if viral load is undetectable.
    - The member has a history of receiving Zynteglo, any prior gene therapy, or allogenic hematopoietic stem cell transplant (HSCT).
    - The member has clinical evidence of advanced liver disease by biopsy (e.g. bridging fibrosis, cirrhosis) or distinct findings of cirrhosis by MRI or CT.
    - The member has aspartate transferase (AST), alanine transaminase (ALT), or direct bilirubin values greater than three times the upper limit of normal.
    - The member has baseline prothrombin time (PT) or partial thromboplastin time (PTT) greater than 1.5 times the upper limit of normal.
    - The member has severely elevated iron in the heart (i.e., member with cardiac T2* less than 10 msec by magnetic resonance imaging [MRI]).

Medicare Variation
Mass General Brigham Health Plan uses guidance from the Centers for Medicare and Medicaid Services (CMS) for coverage determinations for its Medicare Advantage plan members. National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs) and documentation included in the Medicare manuals are the basis for coverage determinations. When there is no guidance from CMS for the requested service, Mass General Brigham Health Plan's medical policies are used for coverage determinations. **At the time of Mass General Brigham Health Plan's most recent policy review, Medicare has no NCD/LCD for Zynteglo.**

MassHealth variation
Prior authorization requests for Zynteglo for Mass General Brigham ACO members should be submitted to the MassHealth Drug Utilization Review Program. Criteria for Zynteglo are found in Table 45: Beta Thalassemia, Myelodysplastic Syndrome, and Sickle Cell Disease Agents.

CPT/HCPC Codes

Authorized Code	Code Description

38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
J3393	Injection, betibeglogene autotemcel, per treatment

Summary of Evidence

Zynteglo (Betibeglogene Autotemcel, beti-cel) is an FDA-approved gene therapy for transfusion-dependent β-thalassemia (TDT) in patients without a β0/β0 genotype, designed as a one-time curative treatment. Clinical trials, including Northstar (HGB-204, Kwiatkowski et al. 2019), Northstar-2 (HGB-207, Locatelli et al. 2022), and Northstar-3 (HGB-212, Lal et al. 2019), assessed its efficacy and safety. These non-randomized, open-label, multicenter studies enrolled 89 patients aged 4–34 years across 15 sites in North America, Europe, and Asia-Pacific, excluding those with significant organ dysfunction or severe concurrent conditions. Transfusion dependence was defined as requiring ≥8 transfusions or ≥100 mL/kg/year of packed red blood cells in the two years before enrollment. A significant proportion (30–40%) had undergone splenectomy, influencing the safety evaluation due to increased infection risk.

Efficacy results demonstrated that 91% of non-β0/β0 patients in Northstar-2 and 67% of β0/β0 patients in Northstar-3 achieved transfusion independence (≥12 months with Hb ≥9 g/dL). Median time to transfusion independence was 3–4 months, with a median duration of response of 26.3 months. Confidence intervals confirmed statistical robustness ($p < 0.001$ for primary endpoints). Outcomes in pediatric patients were similar to those in adults. Secondary endpoints showed reductions in transfusion volume, normalization of iron levels, and quality-of-life improvements on SF-36 scores, correlating with decreased hospital visits and better physical and mental health.

The safety profile was consistent with busulfan conditioning, with common adverse events including anemia, thrombocytopenia, and infusion-related reactions. Serious risks included secondary malignancies and hematologic toxicities, prompting a boxed warning for myelodysplastic syndromes (MDS). Long-term follow-up continues to assess the potential for insertional mutagenesis. Zynteglo's $2.8 million price tag reflects its transformative potential, with market forecasts suggesting broad payer support due to its cost-offsetting benefits, including reduced transfusion-related complications and improved patient independence. However, challenges remain with its high upfront cost, long-term safety monitoring, and emerging competition from alternative gene-editing therapies. Future studies and real-world evidence will refine its positioning in therapy. Regulatory approvals (Bluebird Bio, 2022) and the 2021 Thalassemia International Federation guidelines support its integration into TDT care, although challenges such as cost, accessibility, and long-term management persist. An Institute for Clinical and Economic Review cost-effectiveness analysis concluded that the cost-effectiveness of beti-cel is approximately $95,000/quality-adjusted life year from the health care system's perspective, and thus meets the traditional cost-effectiveness threshold (Lancaster et al. 2022).

Mass General Brigham Health Plan considers beti-cel to be medically necessary for members with TBT who meet criteria based on inclusion criteria in the pivotal Northstar studies.

Effective

April 2025: Annual Review. Codes updated. MassHealth variation updated to include new prior authorization process.
March 2025: Ad hoc update. Summary of evidence added. References updated.
February 2025: Ad hoc update. Removed NCD for Chimeric Antigen Receptor T-cell Therapy from policy. References updated.
September 2024: Ad hoc update.
August 2024: Code update, retroactive to 7/1/2024.
April 2024: Annual Review. Medicaid variation added. Codes added to code list.
May 2023: Effective date.

References

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