Harvard Pilgrim Health Care | TUFTS Health Plan

Medical Necessity Guidelines
Medical Benefit Drugs

Zynteglo® (betibeglogene autotemcel)

Effective: January 1, 2026

Prior Authorization Required If REQUIRED, submit supporting clinical documentation pertinent to service request.	Yes ☒ No ☐

Applies to:

Commercial Products

☒ Harvard Pilgrim Health Care Commercial products; Fax 617-673-0988
☒ Tufts Health Plan Commercial products; Fax 617-673-0988

Public Plans Products

☒ Tufts Health Direct – A Massachusetts Qualified Health Plan (QHP) (a commercial product); Fax 617-673-0988
☐ Tufts Health Together – MassHealth Accountable Care Partnership Plans; Fax 617-673-0939
☒ Tufts Health RITogether – A Rhode Island Medicaid Plan; Fax 617-673-0939
☐ Tufts Health One Care-- A dual-eligible product; Fax 617-673-0956

Senior Products

☐ Tufts Health Plan Senior Care Options (SCO), (a dual-eligible product); Fax 617-673-0956
☐ Tufts Medicare Preferred HMO, (a Medicare Advantage product); Fax 617-673-0956
☐ Tufts Medicare Preferred PPO, (a Medicare Advantage product); Fax 617-673-0956

Note: While you may not be the provider responsible for obtaining prior authorization, as a condition of payment you will need to ensure that prior authorization has been obtained.

Overview

Beta-thalassemia is a type of inherited blood disorder that causes a reduction of normal hemoglobin and red blood cells in the blood, through mutations in the beta-globin subunit, leading to insufficient delivery of oxygen in the body. The reduced levels of red blood cells can lead to a number of health issues including dizziness, weakness, fatigue, bone abnormalities and more serious complications. Transfusion-dependent beta-thalassemia, the most severe form of the condition, generally requires life-long red blood cell transfusions (usually every 2 to 5 weeks) as the standard course of treatment. These regular transfusions can be associated with multiple health complications of their own, including problems in the heart, liver and other organs due to an excessive build-up of iron in the body.

Zynteglo was approved by the FDA on August 17, 2022 for the treatment of adult and pediatric patients with beta thalassemia who require regular blood cell (RBC) transfusions. The product was approved for single intravenous administration only; repeat administration of Zynteglo and its use for the treatment of other indications have not been evaluated.

Zynteglo gene therapy involves inserting a copy of a functional copy of the human beta-globin (HBB) gene into a patient's hematopoietic stem cells outside of the body using a lentiviral vector and then transplanting the modified stem cells back into the patient's blood stream, with the aim that the functional HBB gene will result in normal beta-globin protein expression. The use of autologous stem cells in gene replacement therapy removes the need for a compatible stem cell donor which has limited the ability of individuals to receive allogenic SCT. Lentivirus factors are used because they are capable of accepting the insertion and complex DNA sequences.

Food and Drug Administration (FDA) Approved Indications:

- 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.

Zynteglo works by inserting 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. 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 Zynteglo)

- Myeloablative conditioning using busulfan
- Zynteglo intravenous infusion
- Hospitalization for 3 to 6 weeks after infusion. In clinical trials, the median duration of hospitalization was 45 days from conditioning to discharge

Note: Zynteglo can only be administered at a Zynteglo Qualified Treatment Center (QTC). Each Zynteglo QTC has been carefully selected based on their expertise in areas such as transplant, cell and gene therapy. For information on locating a Zynteglo Qualified Treatment Center, please go to https://www.zynteglo.com/treatment-center-locator or call 1-833-888-NEST (6378).

Clinical Guideline Coverage Criteria

The Plan may cover a one-time infusion of Zynteglo for Members when all of the following criteria are met:

1. The provider attests that the member has a diagnosis of transfusion dependent beta thalassemia* ("β -Thalassemia Major" or "TDT")

   ***Note:** *Transfusion dependance is defined as: a history of ≥ 100mL/kg/year of pRBCs in the two (2) years preceding enrollment, or ≥8 transfusions of pRBCs per year in the prior two (2) years.*

   AND

2. The Member is between 4 and 50 years of age at the time of treatment decision/consent.

   AND

3. The Member must weigh at least 6 kg and be able to provide at least 12 million CD34+ cells per kg for stem cell harvest.

   AND

4. The Member is clinically stable and would be considered a candidate for allogenic hematopoietic stem cell transplantation (HSCT), but ineligible due to the absence of an HLA-matched family donor or any other condition(s) that the provider attests which makes the member ineligible for HSCT.

   AND

5. The Member has not had a prior HSCT.

   AND

6. The Member does not have an active bacterial, viral, fungal, or parasitic infection.

   AND

7. The Member does not have a white blood cell (WBC) count less than 3×10^9/L, ***and/or*** platelet count less than 100×10^9/L not related to hypersplenism.

   AND

8. The Member does not have:
   a. 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***
   b. Any myeloproliferative or significant immunodeficiency disorder.

   ***Note:** *Any prior malignancy must be resolved with no evidence of recurrence for 3 years.*

   AND

9. The Member does not have a parent or sibling with a known Familial Cancer Syndrome (including 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.

   AND

10. The Member does not have a history of major organ damage including **ONE** (1) *or more* of the following:
    a. Advanced liver disease as defined by **ONE** (1) of the following*:*
       i. Persistent aspartate transaminase (AST), alanine transaminase (ALT) or direct bilirubin values greater than three (3) x the upper limit of normal (ULN), ***or***
       ii. Baseline prothrombin time (PT) or partial thromboplastin time (PTT) greater than 1.5 × the ULN, ***or***
       iii. Magnetic Resonance Imaging (MRI) / Computerized Tomography (CT) of the liver demonstrating clear evidence of cirrhosis, ***or***
       iv. Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis. (Liver Biopsy will only be performed if MRI of liver suggests active hepatitis, significant fibrosis, inconclusive evidence of cirrhosis, or liver iron concentration greater than or equal to 15 mg/g for members 18 years of age and older*.

    ***Note:** *MRI findings suggestive of active hepatitis, significant fibrosis; inconclusive evidence of cirrhosis or liver iron concentration greater than or equal to 15 mg/g does not require follow up liver biopsy for members under the age of 18 years.*

    OR

b. Cardiac impairment as defined by:
    i. Cardiac T2*-weighted imaging <10 ms by magnetic resonance imaging (MRI).

OR

c. Renal impairment as defined by:
    i. Baseline eGFR < 60mL/min/1.73m^2

AND

11. The provider attests that there is no other evidence of severe iron overload.

AND

12. The Member does not test positive for HIV-1 and HIV-2, hepatitis B virus (HBV)*, or hepatitis C (HCV)*.

    Note: *Members who have been vaccinated against hepatitis B [hepatitis B surface antibody (HBsAb)-positive] or members with positive hepatitis B core and/or hepatitis B-e antibodies are also eligible provided viral load is negative by quantitative polymerase chain reaction [qPCR]. Also note that members who are positive for anti-hepatitis C antibody are eligible as long as they have a negative HCV viral load by qPCR).*

AND

13. The Member has documentation of ***ONE*** (1) of the following performance scores:
    a. A score of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status
    b. A score of 80 or higher on the Karnofsky Performance Scale if 16 years of age or older
    c. A score of 80 or higher on the Lansky Performance Scale if less than 16 years of age.

AND

14. The prescribing physician is a hematologist who specializes in the treatment of Beta-Thalassemia.

AND

15. The Member will have treatment administered at a Zynteglo Qualified Treatment Center (Zynteglo QTC).

Limitations

- Zynteglo will only be approved for an FDA-approved indication(s) as per the product label. All other uses are considered experimental or investigational.
- Authorization of Zynteglo will be limited to one treatment per lifetime. Any Member who has previously received Zynteglo through a clinical trial or while insured under another health plan will not be approved for a repeat course of treatment. The safety and efficacy of repeat doses of Zynteglo has not been evaluated.
- Zynteglo will not be approved for any member who is a recipient of prior gene therapy.

Codes

The following code(s) require prior authorization:

Table 1: HCPCS Codes

HCPCS Codes	Description
J3393	Injection, betibeglogene autotemcel, per treatment

References:

1. FDA Approves First Cell-Based Gene Therapy to Treat Adult and Pediatric Patients with Beta-thalassemia Who Require Regular Blood Transfusions. US Food and Drug Administration. August 17, 2022. Accessed online August 18, 2022 at https://web.archive.org/web/20220821044703/http:/www.fda.gov/news-events/press-announcements/fda-approves-first-cell-based-gene-therapy-treat-adult-and-pediatric-patients-beta-thalassemia-who
2. Clinical Study Protocol HGB-207.Cambridge, MA; bluebird bio, inc.; 27 January 2016
3. 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).
4. Lentiglobin and Luspatercept for Beta-Thalassemia: Effectiveness and Value. Institute for Clinical and Economic Review (ICER).January 6, 2020.
5. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene Autotemcel Gene Therapy for Non-β 0 /β0 Genotype β-Thalassemia. N Engl J Med. 2022;386(5):415-427.
6. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Supplementary Appendix: Betibeglogene Autotemcel Gene Therapy for Non-β 0 /β0 Genotype β-Thalassemia. N Engl J Med. 2022;386(5):415-427.
7. Zynteglo (betibeglogene autotemcel) [prescribing information]. Somerville, MA; bluebird bio, inc.; August 2022.
8. Taher AT, et. al. editors. Guidelines for the Management of Transfusion-Dependent β-Thalassaemia (TDT) [Internet]. 5th ed. Nicosia, Cyprus: Thalassaemia International Federation; 2025. PMID: 40367250.

9. Kansal AR, et. al. Economic evaluation of betibeglogene autotemcel (Beti-cel) gene addition therapy in transfusion-dependent β-thalassemia. J Mark Access Health Policy. 2021 Jun 7;9(1):1922028. doi: 10.1080/20016689.2021.1922028. PMID: 34178295; PMCID: PMC8205006.
10. Whitney D, et. al. Drug product attributes predict clinical efficacy in betibeglogene autotemcel gene therapy for β-thalassemia. Mol Ther Methods Clin Dev. 2023 Nov 10;31:101155. doi: 10.1016/j.omtm.2023.101155. PMID: 38074412; PMCID: PMC10709156.

Approval And Revision History

March 15, 2023: Reviewed and Approved at Medical Policy Approval Committee (MPAC)

Subsequent endorsement date(s) and changes made:

- Originally approved November 16, 2022 by MPAC committees effective January 1, 2023
- Administrative update: March 2023 added Medical Benefit Drugs to title, updated MATogether and RITogether fax numbers to 617-673-0939
- March 17, 2023: Updated criteria 1. Removed “And does not have the β/β genotype of the HBB gene”, effective July 1, 2023
- November 16, 2023: Annual review, no changes
- November 2023: Rebranded Unify to One Care effective January 1, 12024
- June 2024: Administrative update: Zynteglo code J3393 added effective July 1, 2024
- November 21, 2024: Reviewed by MPAC, renewed without changes, effective January 1, 2025.
- November 19, 2025: Reviewed by MPAC for annual review, renewed without changes, references updated, effective January 1, 2026
- December 2025: Administrative updates effective January 1, 2026

Background, Product and Disclaimer Information

Medical Necessity Guidelines are developed to determine coverage for benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. We make coverage decisions using these guidelines, along with the Member’s benefit document, and in coordination with the Member’s physician(s) on a case-by-case basis considering the individual Member's health care needs.

Medical Necessity Guidelines are developed for selected therapeutic or diagnostic services found to be safe and proven effective in a limited, defined population of patients or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in our service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. We revise and update Medical Necessity Guidelines annually, or more frequently if new evidence becomes available that suggests needed revisions.

For self-insured plans, coverage may vary depending on the terms of the benefit document. If a discrepancy exists between a Medical Necessity Guideline and a self-insured Member’s benefit document, the provisions of the benefit document will govern. For Tufts Health Together (Medicaid), coverage may be available beyond these guidelines for pediatric members under age 21 under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefits of the plan in accordance with 130 CMR 450.140 and 130 CMR 447.000, and with prior authorization.

Treating providers are solely responsible for the medical advice and treatment of Members. The use of this guideline is not a guarantee of payment or a final prediction of how specific claim(s) will be adjudicated. Claims payment is subject to eligibility and benefits on the date of service, coordination of benefits, referral/authorization, utilization management guidelines when applicable, and adherence to plan policies, plan procedures, and claims editing logic.