MVP Health Care Medical Policy

Medicare Part B: Zynteglo

Type of Policy: **Drug/Medical Therapy**
Prior Approval Date: **01/01/2025**
Approval Date: **12/01/2025**
Effective Date: **02/01/2026**
Related Policies: **N/A**

Refer to the MVP Medicare website for the Medicare Part D formulary and Part D policies.

Refer to relevant CMS LCDs/NCDs/Policy Articles for most up to date Medicare Part B guidance if available.

Drugs Requiring Prior Authorization under the medical benefit

J3393 Zynteglo (betibeglogene autotemcel)

Overview/Summary of Evidence

Zynteglo is a cell-based gene therapy that is indicated for the treatment of pediatric and adult members with beta-thalassemia who require regular red blood cell (RBC) transfusion.

Indications/Criteria

Zynteglo may be considered for coverage when the following criteria are met:

A. Initial Approval Criteria
   a. Submission of medical records (chart notes) related to the medical necessity criteria is REQUIRED on all requests for authorizations. Records will be reviewed at the time of submission. Please provide documentation

related to diagnosis, step therapy, and clinical markers (i.e., genetic, and mutational testing) supporting initiation when applicable.

b. Coverage is provided in the following conditions:
    i. Member is at least 4 years of age; **AND**
    ii. Member has been screened for hepatitis B virus (HBV), hepatitis C virus (HCV), human T-lymphotrophic virus 1 & 2 (HTLV-1/HTLV-2), and human immunodeficiency virus (HIV) in accordance with clinical guidelines prior to collection of cells (leukapheresis); **AND**
    iii. Member has not used prophylactic HIV anti-retroviral medication or hydroxyurea within 30 days prior to mobilization (or for the expected duration for elimination of those medications) and until all cycles of apheresis are completed
        - Note: if a member requires anti-retrovirals for HIV prophylaxis, confirm a negative test for HIV before beginning mobilization; **AND**
    iv. Iron chelation therapy has been discontinued for at least 7 days prior to initiating myeloablative conditioning therapy; **AND**
    v. Females of reproductive potential have a negative pregnancy test prior to start of mobilization and re-confirmed prior to conditioning procedures and again before administration of betibeglogene autotemcel; **AND**
    vi. Used as single agent therapy (not applicable to lymphodepleting or bridging therapy while awaiting manufacture); **AND**
    vii. Provider attestation that the member will receive periodic life-long monitoring for hematological malignancies; **AND**
    viii. Provider attestation that the member is eligible to undergo hematopoietic stem cell transplant (HSCT) and has not had prior HSCT or other gene-therapy; **AND**
    ix. Member has a documented diagnosis of beta thalassemia (excludes alpha-thalassemia and hemoglobin S/ß-thalassemia variants) as outlined by the following:
        - Member diagnosis is confirmed by HBB sequence gene analysis showing biallelic pathogenic variants; **OR**
        - Member has severe microcytic hypochromic anemia, anisopoikilocytosis with nucleated red blood cells on peripheral blood smear, and hemoglobin analysis that reveals decreased amounts or complete absence of hemoglobin A and increased amounts of hemoglobin F; **AND**

- Member has transfusion-dependent disease defined as 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 therapy; **AND**
- Member does not have any of the following:
    - Severely elevated iron in the heart (i.e., members with cardiac T2* less than 10 msec by magnetic resonance imaging [MRI]); **OR** Advanced liver disease; **OR**
    - Members with an MRI of the liver with results demonstrating liver iron content ≥ 15 mg/g (unless biopsy confirms absence of advanced disease)

Zynteglo will be approved as a **one-time dose** and will not need to be continued for maintenance. Coverage is contingent on eligibility at the time of infusion

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Exclusions

The use of Zynteglo will not be covered for the following situations:

- More than one treatment per lifetime
- Requests for replacement due to lost or damaged product will not be covered
- Age, dose, frequency of dosing, and/or duration of therapy outside of FDA approved package labeling

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Appendix I: Dosing and Administration

A. Dosing Limits
    a. Quantity Limit (max daily dose) [NDC Unit]: A single dose of Zynteglo containing a minimum of 5.0×10^6 CD34+ cells/kg of body weight, in one or more infusion bags.
    b. Max Units (per dose and over time) [HCPCS Unit]:A single dose of Zynteglo containing a minimum of 5.0×10^6 CD34+ cells/kg of bodyweight, in one or more infusion bags

Indication	Dose
Beta Thalassemia	**Mobilization and Apheresis** – Patients are required to undergo HSC mobilization followed by apheresis to obtain CD34+ cells for product manufacturing. The target number of CD34+ cells to be collected is ≥ 12×10^6 CD34+ cells/kg. *(**Note**: If the minimum dose of 5.0×10^6 CD34+ cells/kg is not met, the patient may undergo additional cycles of mobilization and apheresis, separated by at least 14 days, in order to obtain more cells for additional manufacture. Up to two drug product lots may be administered to meet the target dose.)* – A back-up collection of CD34+ cells of ≥ 1.5×10^6 CD34+ cells/kg (if collected by apheresis) or > 1.0×10^8 TNC/kg (Total Nucleated Cells, if collected by bone marrow harvest) is required. These cells must be collected from the patient and be cryopreserved prior to myeloablative conditioning. The back-up collection may be needed for rescue treatment if there is: o Compromise of hematopoietic stem cells or Zynteglo before infusion o Primary engraftment failure o Loss of engraftment after infusion with Zynteglo – Note: G-CSF and plerixafor were used for mobilization **Myeloablative Conditioning** – Full myeloablative conditioning must be administered before infusion of Zynteglo. Consult prescribing information for the myeloablative conditioning agent(s) prior to treatment. – Prophylaxis for hepatic veno-occlusive disease (VOD) is recommended and prophylaxis for seizures should be considered, as appropriate. – Do not begin myeloablative conditioning until the complete set of infusion bag(s) constituting the dose of Zynteglo has been received and stored at the treatment center and the availability of the back-up collection is confirmed. After completion of the myeloablative conditioning, allow a minimum of 48 hours of washout before Zynteglo infusion. – Note: busulfan was used for myeloablative conditioning **Administration** – Verify that the patient's identity matches the unique patient identification information on the Zynteglo infusion bag(s) prior to infusion. – Do not sample, alter, or irradiate Zynteglo. – Do not use an in-line blood filter or an infusion pump. – Administer each infusion bag of Zynteglo via intravenous infusion over a period of less than 30 minutes. Product must be administered within 4 hours after thawing.
For autologous use only. For intravenous use only. – 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 prior to infusion, do not re-freeze after thawing. Do not irradiate as this could lead to inactivation. – 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.	

References

1. Zynteglo [package insert]. Somerville, MA; Bluebird bio, Inc: August 2022. Accessed August 2022.

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4. Origa R. Beta-Thalassemia. 2000 Sep 28 [Updated 2021 Feb 4]. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from https://www.ncbi.nlm.nih.gov/books/NBK1426/. Accessed August 2022.

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6. Schneiderman, J, Thompson AA, Walters MC, et al. Interim Results from the Phase 3 Hgb207(Northstar-2) and Hgb-21) (Northstar-3) Studies of Betibeglogene Autotemcel Gene Therapy (LentiGlobin) for the Treatment of Transfusion-Dependent β-Thalassemia. Bio Blood Marrow Trnsplt. Volume 26, Issue 3, Supplement, March 2020,Pages S87-S88. https://doi.org/10.1016/j.bbmt.2019.12.588.

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