Zynteglo® (betibeglogene autotemcel)
(Intravenous)

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I. Length of Authorization [1]

Coverage will be provided for one treatment course (1 dose of Zynteglo) and may not be renewed.

II. 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 body weight, in one or more infusion bags

III. Initial Approval Criteria [1]

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. Please provide documentation via direct upload through the PA web portal or by fax.

Coverage is provided in the following conditions:

Use for indications outside of FDA-approved labeled indications does NOT meet medical criteria for coverage and will be considered investigational, thus will NOT be covered.

- Patient is at least 4 years of age; **AND**
- Patient 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**
- Patient 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 patient requires anti-retrovirals for HIV prophylaxis, confirm a negative test for HIV before beginning mobilization); **AND**

- Iron chelation therapy has been discontinued for at least 7 days prior to initiating myeloablative conditioning therapy; **AND**
- 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**
- Used as single agent therapy (not applicable to lymphodepleting or bridging therapy while awaiting manufacture); **AND**
- Provider attests that informed consent was obtained from the patient/family, including potential risk for hematologic malignancy; **AND**
- Patient is eligible to undergo hematopoietic stem cell transplant (HSCT); **AND**
- Patient has not had prior HSCT or other gene-therapy; **AND**

Beta Thalassemia † Φ [1,4-7]

- Patient has a documented diagnosis of beta thalassemia (excludes alpha-thalassemia and hemoglobin S/ß-thalassemia variants) as outlined by the following:
    - Patient diagnosis is confirmed by *HBB* sequence gene analysis showing biallelic pathogenic variants; **OR**
    - Patient 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**
- Patient 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**
- Patient does not have any of the following:
    - 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; **OR**
    - Patients with an MRI of the liver with results demonstrating liver iron content ≥ 15 mg/g (unless biopsy confirms absence of advanced disease)

† FDA Approved Indications; **‡** Compendia Recommended Indication(s); **Φ** Orphan Drug

IV. Renewal Criteria [1]

Coverage cannot be renewed.

V. Dosage/Administration [1]

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: ○ Compromise of hematopoietic stem cells or Zynteglo before infusion ○ Primary engraftment failure ○ 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.

VI. Billing Code/Availability Information

HCPCS Code:

- J3590 – Unclassified biologics
- C9399 – Unclassified drugs or biologicals *(for hospital outpatient use ONLY)*

NDC:

- Zynteglo up to 4 infusion bags, 20 mL/infusion bag, overwrap, and metal cassette: 73554-3111-xx

VII. References

1. Zynteglo [package insert]. Somerville, MA; Bluebird bio, Inc: August 2022. Accessed March 2023.
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3. Galanello R and Origa R. Beta-thalassemia. *Orphanet J Rare Dis.* 2010 May 21;5:11. Available at: https://ojrd.biomedcentral.com/articles/10.1186/1750-1172-5-11. Accessed March 2023.
4. Origa R. Beta-Thalassemia. 2000 Sep 28 [Updated 2021 Feb 4]. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1426/. Accessed March 2023.
5. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene Autotemcel Gene Therapy for Non-β(0)/β(0) Genotype β-Thalassemia. N Engl J Med. 2022 Feb 3;386(5):415-427. doi: 10.1056/NEJMoa2113206. Epub 2021 Dec 11.
6. Schneiderman, J, Thompson AA, Walters MC, et al. Interim Results from the Phase 3 Hgb-207 (Northstar-2) and Hgb-212 (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
7. Magrin E, Semeraro M, Hebert N, et al. Long-term outcomes of lentiviral gene therapy for the β-hemoglobinopathies: the HGB-205 trial. Nat Med. 2022 Jan;28(1):81-88. doi: 10.1038/s41591-021-01650-w. Epub 2022 Jan 24.
8. Beaudoin FL, Richardson M, Synnott PG, et al. Betibeglogene Autotemcel for Beta Thalassemia: Effectiveness and Value; Final Evidence Report. Institute for Clinical and Economic Review, July 19, 2022. https://icer.org/beta-thalassemia-2022/#timeline

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
D56.1	Beta thalassemia

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC