Zynteglo® (betibeglogene autotemcel)
(Intravenous)

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I. Length of Authorization

- Initial: Prior authorization validity will be provided initially for one treatment course (1 dose of Zynteglo).
- Renewal: Prior authorization validity may NOT be renewed.

II. Dosing Limits

Max Units (per dose and over time) [HCPCS Unit]:

- 1 billable unit (1 treatment)

III. Initial Approval Criteria [1]

Submission of supporting clinical documentation (including but not limited to medical records, chart notes, lab results, and confirmatory diagnostics) related to the medical necessity criteria is REQUIRED on all requests for authorizations. Records will be reviewed at the time of submission as part of the evaluation of this request. 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. Failure to submit the medical records may result in the denial of the request due to inability to establish medical necessity in accordance with policy guidelines.

Prior authorization validity 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**
- Provider has considered use of prophylaxis therapy for seizures prior to initiating myeloablative conditioning; **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**
- Provider will confirm that patient will not be administered live vaccines concurrently while immunosuppressed; **AND**
- Patient does not have a history of hypersensitivity to dimethyl sulfoxide (DMSO); **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 apheresis); **AND**
- Iron chelation therapy has been discontinued for at least 7 days prior to initiating myeloablative conditioning therapy and myelosuppressive iron chelators will be avoided for 6 months post-treatment; **AND**
- Patient has not received other gene therapies used for treatment of beta thalassemia [e.g., Casgevy™ (exagamglogene autotemcel), etc.]**; **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**
- Patient does not have a known and available suitable 10/10 human leukocyte antigen matched related donor willing to participate in an allogeneic HSCT; **AND**

*** Requests for subsequent use of betibeglogene after receipt of other gene therapies used for treatment of beta thalassemia (e.g., exagamglogene, etc.) will be evaluated on a case-by-case basis*

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, absence of iron deficiency, anisopoikilocytosis with nucleated red blood cells on peripheral blood smear, and hemoglobin analysis that reveals decreased amounts or complete absence of hemoglobin A (HbA) and increased HbA_2 with or without increased amounts of hemoglobin F (HbF); **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 will be maintained at a Hb ≥ 11 g/dL for 30 days prior to mobilization and 30 days prior to myeloablative conditioning; **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 (i.e., persistent AST, ALT, or direct bilirubin value > 3 times the upper limit of normal (ULN), baseline prothrombin time or partial thromboplastin time > 1.5 times the ULN, MRI of the liver demonstrated cirrhosis, or liver biopsy demonstrated bridging fibrosis, active hepatitis, or cirrhosis); **OR**
  - MRI of the liver with results demonstrating liver iron content ≥ 15 mg/g (unless biopsy confirms absence of advanced disease)

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

IV. Renewal Criteria [1]

Duration of authorization has not been exceeded *(refer to Section I)*.

V. Dosage/Administration [1]

Indication	Dose
Beta Thalassemia	Zynteglo is provided as a single dose for intravenous infusion containing a suspension of CD34+ cells in one or more infusion bags to achieve the patient-specific dose. The minimum recommended dose of Zynteglo is 5.0×10^6 CD34+ cells/kg
– Granulocyte-colony stimulating factor (G-CSF) and plerixafor should be used for mobilization and busulfan should be used for myeloablative conditioning. – Myeloablative conditioning (e.g., busulfan) should not occur until Zynteglo is received and stored at the treatment center and availability of the back-up cell collection is confirmed. – Prophylaxis for hepatic veno-occlusive disease (VOD) is recommended prior to initiating myeloablative conditioning. – After completion of the myeloablative conditioning, allow a minimum of 48 hours of washout before Zynteglo infusion. – Zynteglo is for autologous use only. Before infusion, confirm that the patient's identity matches the unique patient identifiers on the Zynteglo infusion bag(s). Do not infuse if the information on the patient-specific label does not match the intended patient.	

VI. Billing Code/Availability Information

HCPCS Code:

- J3393 – Injection, betibeglogene autotemcel, per treatment; 1 billable unit = 1 treatment

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 October 2025.
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4. Langer AL. Beta-Thalassemia. 2000 Sep 28 [Updated 2024 Feb 8]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1426/. Accessed October 2025.
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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 A – Non-Quantitative Treatment Limitations (NQTL) Factor Checklist

Non-quantitative treatment limitations (NQTLs) refer to the methods, guidelines, standards of evidence, or other conditions that can restrict how long or to what extent benefits are provided under a health plan. These may include things like utilization review or prior authorization. The utilization management NQTL applies comparably, and not more stringently, to mental health/substance use disorder (MH/SUD) Medical Benefit Prescription Drugs and medical/surgical (M/S) Medical Benefit Prescription Drugs. The

table below lists the factors that were considered in designing and applying prior authorization to this drug/drug group, and a summary of the conclusions that Prime's assessment led to for each.

Factor	Conclusion
Indication	Yes: Consider for PA
Safety and efficacy	No: PA not a priority
Potential for misuse/abuse	No: PA not a priority
Cost of drug	Yes: Consider for PA

Appendix 1 – Covered Diagnosis Codes

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

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

The preceding information is intended for non-Medicare coverage determinations. 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 Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied 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
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
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)

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
15	KY, OH	CGS Administrators, LLC