Clinical Policy: Betibeglogene Autotemcel (Zynteglo)

Reference Number: CP.PHAR.545
Effective Date: 11.01.22
Last Review Date: 08.26
Line of Business: Commercial, HIM/ICHRA, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Betibeglogene autotemcel (Zynteglo®) is an autologous hematopoietic stem cell-based gene therapy.

FDA Approved Indication(s)

Zynteglo is indicated for the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results, or other clinical information) supporting that member has met all approval criteria.

All requests reviewed under this policy **require Precision Drug Action Committee (PDAC) Utilization Management Review**. Refer to CC.PHAR.21 for process details.

It is the policy of health plans affiliated with Centene Corporation® that Zynteglo is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

**Only for initial treatment dose; subsequent doses will not be covered.*

A. β-Thalassemia (must meet all)**:**

1. Diagnosis of β-thalassemia with genetic confirmation (*see Appendix E*);
2. Prescribed by or in consultation with a hematologist and transplant specialist;
3. Age ≥ 4 years and ≤ 50 years;
4. Documentation of one of the following (a or b):
   a. Receipt of ≥ 100 mL/kg packed red blood cells (pRBC) per year for the previous two years (*see Appendix D*);
   b. Receipt of ≥ 8 transfusions of pRBC per year for the previous two years (*see Appendix D*);
5. Attestation from transplant specialist for both of the following (a and b):
   a. Member understands the risks and benefits of alternative therapeutic options such as allogeneic hematopoietic stem cell transplantation (HSCT);
   b. Member is clinically stable and eligible to undergo myeloablative conditioning and HSCT;
6. Member has not received prior allogeneic HSCT;
7. Member has not received prior gene therapy;
8. Member does not have advanced liver disease (*see Appendix D*);

9. Documentation from within the last 6 months that the member is negative for the presence of HIV type 1 or 2;
10. Member does not have any prior or current malignancy;
11. Dose contains a minimum of 5 x 10^6 CD34+ cells/kg.

Approval duration: 6 months (one-time infusion per lifetime)

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. β-Thalassemia

1. Continued therapy will not be authorized as Zynteglo is indicated to be dosed one time only.

Approval duration: Not applicable

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line

of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
HIV: human immunodeficiency virus
HSCT: hematopoietic stem cell transplantation
pRBC: packed red blood cells
RBC: red blood cell

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: General Information

- Conversion of RBC units from mL: 1 RBC unit in these criteria refers to a quantity of pRBC approximately 200-350 mL.
  - For sites who use transfusion bags within this range, or ≥ 350 mL, the conversion in units should be done by dividing the volume transfused to the patient by 350 mL.
  - For sites who use transfusion bags < 200 mL, the conversion in units should be done by dividing the volume transfused to the patient by 200 mL.
- Examples of advanced liver disease include, but are not limited to, the following:
  - Cirrhosis
  - Active hepatitis
  - Bridging fibrosis
  - Fatty liver disease

Appendix E: Genetic Confirmation of β-Thalassemia

β-Thalassemia Genotype Examples
β^0/β^0
β^0/β^+
β^+/β^+
β^E/β^0
β^+ IVS1-110/β^+ IVS1-110
β^0 /β^+ IVS1-110
β^E/β^0

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
β-thalassemia	Minimum dose: 5×10^6 CD34+ cells/kg of body weight IV	Not applicable

VI. Product Availability

Single-dose cell suspension: up to four infusion bags of transduced CD34+ cells in cryopreservation solution labeled for the specific recipient

VII. References

1. Zynteglo Prescribing Information. Somerville, MA: bluebird bio, Inc.; August 2022. Available at: https://www.bluebirdbio.com/-/media/bluebirdbio/CorporateCOM/Files/Zynteglo/ZYNTEGLO_Prescribing_Information.pdf. Accessed April 15, 2026.
2. Kwiatkowski JL, Walters MC, Hongeng S, et al. Betibeglogene autotemcel gene therapy in patients with transfusion-dependent, severe genotype β-thalassaemia (HGB-212): a non-randomised, multicentre, single-arm, open-label, single-dose, phase 3 trial. *Lancet*. 2024;404(10468):2175-2186.
3. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene autotemcel gene therapy for non-β0/β0 genotype β-thalassemia. N Engl J Med. 2022;386(5):415-427.
4. Porter JB, Thompson AA, Walters MC, et al. Improvement in erythropoiesis in patients with transfusion dependent β-thalassemia following treatment with betibeglogene autotemcel (LentiGlobin for β-thalassemia) in the phase 3 HGB-207 study. EHA 2020 Virtual Congress Abstract: S296.
5. Taher AT, Farmakis D, Porter JB, et al. Guidelines for the management of transfusion dependent thalassemia (TDT) 5th Edition. Thalassemia International Federation (2025). Available at: https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-transfusion-dependent-β-thalassaemia-5th-edition-2025/. Accessed May 21, 2026.
6. Frangoul H, Stults A, Bruce K, et al. Best practices in gene therapy for sickle cell disease and transfusion-dependent β-thalassemia. Transplant Cell Ther. Published online March 7, 2025. doi:10.1016/j.jtct.2025.02.025

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J3393	Injection, betibeglogene autotemcel, per treatment

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2022 annual review: no significant changes as drug is not yet FDA-approved; references reviewed and updated.	05.03.22	08.22
Drug is now FDA approved – criteria updated per FDA labeling: added transplant specialist involvement as this gene therapy would involve a multidisciplinary team; clarified that receipt of ≥ 8 transfusions annually is an option for members age ≥ 12 years per pivotal trials' protocol and that both transfusion-dependence criteria options are to be measured per year for the previous two years; revised criterion that member is eligible for allogeneic HSCT to include transplant specialist provider attestation that the member both understands the risks and benefits of alternative therapeutic options such as allogeneic HSCT and is clinically stable, and removed "allogeneic" per published pivotal trials inclusion criteria; removed exclusion criteria for hepatitis B and C viruses as these are not excluded per FDA labeling; updated dosing criterion to a minimum dose per FDA labeling; references reviewed and updated.	09.06.22	11.22
3Q 2023 annual review: no significant changes; added additional TDT genotype examples to appendix E (β^{+}/β^{+} and β^{0}/β^{+} IVS1-110); references reviewed and updated	04.24.23	08.23
Added HCPCS code [J3393] and removed HCPCS codes [J3590, C9399].	06.03.24	
3Q 2024 annual review: revised lower age limit to age ≥ 4 years and removed accompanying age < 5 criteria; removed age qualifier of ≥ 12 years for receipt of ≥ 8 transfusions of pRBC per year; added clarification for time component and documentation within the last 6 months for negative HIV test; approval duration extended from 3 months to 6 months to allow for member preparation and adequate time for gene therapy manufacture; added clarification of a one-time dose only for continued authorization; corrected template language for continued therapy; references reviewed and updated.	05.21.24	08.24
3Q 2025 annual review: no significant changes; added template statement requiring medical director review; added criterion for documentation of member's body weight for verification of weight-based dose; references reviewed and updated.	04.14.25	08.25
Updated language under Policy/Criteria to effectively redirect prior authorization reviews to Precision Drug Action Committee (PDAC) Utilization Management Review.	11.04.25	
3Q 2026 annual review: no significant changes; added ICHRA line of business; removed requirement for documentation of body weight; references reviewed and updated.	04.15.26	08.26

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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