Clinical Policy: Betibeglogene Autotemcel (Zynteglo)

Reference Number: ERX.SPA.447
Effective Date: 11.01.22
Last Review Date: 11.22
Line of Business: Commercial, Medicaid

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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. Member meets one of the following (a or b):
   a. Age ≥ 5 years and ≤ 50 years;
   b. If age < 5 years, member meets both of the following (i and ii):
      i. Weight ≥ 6 kg;
      ii. Provider submits medical rationale that member is anticipated to be able to provide at least the minimum number of cells required to initiate the manufacturing process;
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. For age ≥ 12 years: 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 or gene therapy;
7. Member does not have advanced liver disease (*see Appendix D*);
8. Member is not positive for the presence of HIV type 1 or 2;
9. Member does not have any prior or current malignancy;
10. Dose contains a minimum of 5 x 10^6 CD34+ cells/kg.

Approval duration: 3 months (one time infusion per lifetime)

B. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. β-Thalassemia

1. Re-authorization is not permitted.

Approval duration: Not applicable

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 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

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^+ IVS1-110/β^+ IVS1-110
B^E/β^0

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
β-thalassemia	Minimum dose: 5 × 10^6 CD34+ cells/kg	No maximum dose

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 August 17, 2022.
2. ClinicalTrials.gov. A study evaluating the efficacy and safety of the Lentiglobin® BB305 drug product in subjects with transfusion-dependent β-thalassemia, who do not have a β0/β0 genotype. Last updated June 25, 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT02906202. Accessed June 26, 2021.
3. ClinicalTrials.gov. A study evaluating the efficacy and safety of the Lentiglobin® BB305 drug product in subjects with transfusion-dependent β-thalassemia. Last updated June 24, 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT03207009. Accessed June 26, 2021.
4. 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.
5. 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.
6. Cappellini MD, Farmakis D, Porter J, et al. Guidelines for the management of transfusion dependent thalassemia (TDT) 4th Edition. Thalassemia International Federation (2021). Available at: https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-transfusion-dependent-thalassaemia-4th-edition-2021/. Accessed May 3, 2022.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	07.13.21	08.21
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

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.