PROVIDER POLICIES & PROCEDURES

ZYNTEGLO™ (betibeglogene autotemcel)

The primary purpose of this document is to assist providers enrolled in the Connecticut Medical Assistance Program (CMAP) with the information needed to support a medical necessity determination for gene therapy with Zynteglo (betibeglogene autotemcel). By clarifying the information needed for prior authorization of services, HUSKY Health hopes to facilitate timely review of requests so that individuals obtain the medically necessary care they need as quickly as possible.

Beta-thalassemia (β-thalassemia) is a hemoglobinopathy in which the normal ratio of alpha globin to beta globin production is disrupted due to a genetic variant in one or more alpha or beta globin genes. Individuals typically inherit two beta globin genes, one from each parent. β-thalassemia is caused by reduced production of beta chains and accumulation of excess alpha chains, and the severity of disease correlates with the amount of normal beta globin production. Individuals with β-thalassemia who require regular transfusions due to severe anemia and/or significant complications of extramedullary hematopoiesis are referred to as having transfusion-dependent β-thalassemia.

Zynteglo is a single-dose autologous hematopoietic stem cell-based gene therapy indicated for the treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions. It works by adding functional copies of a modified β-globin gene (HbA^{T87Q}) into patients' hematopoietic stem cells through transduction of autologous CD34+ cells with BB305 LVV. The HbA^{T87Q} is designed to correct the β/α-globin imbalance in erythroid cells of patients with β-thalassemia and has the potential to increase functional adult HbA and total Hb to normal levels and eliminate dependence on regular red blood cell transfusions.

CLINICAL GUIDELINE

Coverage decisions for the use of Zynteglo will be made in accordance with the DSS definition of Medical Necessity. The following criteria are guidelines *only*. Coverage decisions are based on an assessment of the individual and their unique clinical needs. If the guidelines conflict with the definition of Medical Necessity, the definition of Medical Necessity shall prevail. The guidelines are as follows:

Treatment with Zynteglo will be considered medically necessary for individuals with *transfusion-dependent β-thalassemia* when ALL of the following criteria are met:

A. The individual is 4 years of age or older; **AND**
B. The individual has a diagnosis of β-thalassemia as confirmed by genetic testing; **AND**
C. The treatment is prescribed by or in consultation with a hematologist; **AND**
D. The treatment will be administered at an authorized treatment center; **AND**
E. The individual requires regular RBC transfusions defined by a history of at least 100 mL/kg/year of RBCs or ≥8 transfusions of RBCs per year for the prior 2 years; **AND**

F. The individual is eligible for a hematopoietic stem-cell transplant (HCST) as determined by the hematologist; **AND**
G. The individual does not have an available 10/10 human leukocyte antigen-matched related donor; **AND**
H. The individual has not previously received a hematopoietic stem-cell transplant; **AND**
I. The individual has not previously received Zynteglo or any other gene therapy; **AND**
J. The individual does not have any of the following:
    a. Advanced liver disease as defined by the following:
        1. Alanine transaminase (ALT) >3 × the upper limit of normal (ULN) or direct bilirubin value >2.5 × ULN; **OR**
        2. Baseline prothrombin time (PT) (international normalized ratio [INR]) >1.5 × ULN, **OR**
        3. History of cirrhosis or any evidence of bridging fibrosis, or active hepatitis on liver biopsy; **AND**
    b. Bacterial, viral, fungal or parasitic infection including HIV-1, HIV-2, hepatitis B or hepatitis C; **AND**
    c. Any prior or current malignancy or myeloproliferative disorder or a significant immunodeficiency disorder; **AND**
K. The provider will follow all FDA recommendations for usage, dosage, preparation, administration, monitoring and patient education.

Investigational and Not Medically Necessary

Zynteglo is considered investigational and therefore not medically necessary for all other indications not specified in this policy.

NOTE: EPSDT Special Provision
Early and Periodic Screening, Diagnosis, and Treatment (EPSDT) is a federal Medicaid requirement that requires the Connecticut Medical Assistance Program (CMAP) to cover services, products, or procedures for Medicaid enrollees under 21 years of age where the service or good is medically necessary health care to correct or ameliorate a defect, physical or mental illness, or a condition identified through a screening examination. The applicable definition of medical necessity is set forth in Conn. Gen. Stat. Section 17b-259b (2011) [ref. CMAP Provider Bulletin PB 2011-36].

PROCEDURE
Prior authorization of Zynteglo is required. Coverage determinations will be based upon a review of requested and/or submitted case-specific information.

The following information is needed to review requests for Zynteglo:
1. Fully completed State of Connecticut, Department of Social Services HUSKY Health Program Zynteglo Prior Authorization Request form (to include physician's order and signature); **AND**
2. Clinical documentation supporting the medical necessity of treatment with Zynteglo should include the following:
    a. Genetic testing results confirming the diagnosis of β-thalassemia; **AND**
    b. Medical record documenting a history of at least 100 mL/kg/year of RBCs or ≥8 transfusions of RBCs per year for the prior 2 years; **AND**
    c. Laboratory data confirming the absence of:

i. HIV-1, HIV-2, HBV, HCV infection; **AND**
ii. Advanced liver disease; **AND**

d. Signed provider attestation confirming the following:
i. The individual is eligible for a hematopoietic stem-cell transplant (HCST); **AND**
ii. The individual does not have an available 10/10 human leukocyte antigen-matched related donor; **AND**
iii. The individual has not previously received a HCST; **AND**
iv. The individual has not previously received Zynteglo or any other gene therapy; **AND**
v. The individual does not have any prior or current malignancy or myeloproliferative disorder or a significant immunodeficiency disorder; **AND**

3. Other information as requested.

Requesting Authorization
Requests for the prior authorization of Zynteglo must be submitted by the ordering physician and faxed to the number listed on the request form. Questions regarding this form should be directed to the HUSKY Health Program Utilization Management Department at 1.800.440.5071 (select option for medical authorizations).

Initial Authorization
If approved, authorization will be given for a one-time, single-dose intravenous infusion of Zynteglo.

Reauthorization
Zynteglo is indicated as a one-time infusion only. Repeat administration of Zynteglo is not supported by FDA labeling or compendia and is therefore not considered medically necessary.

EFFECTIVE DATE
This Policy for the prior authorization of Zynteglo for individuals covered under the HUSKY Health Program is effective May 1, 2025.

LIMITATIONS
N/A

CODES:

Code	Definition
J3393	Injection, betibeglogene autotemcel, per treatment

DEFINITIONS
1. **HUSKY A**: Connecticut children and their parents or a relative caregiver; and pregnant women may qualify for HUSKY A (also known as Medicaid). Income limits apply.
2. **HUSKY B**: Uninsured children under the age of 19 in higher income households may be eligible for HUSKY B (also known as the Children's Health Insurance Program) depending on their family income level. Family cost-sharing may apply.
3. **HUSKY C**: Connecticut residents who are age 65 or older or residents who are ages 18-64 and who are blind, or have another disability, may qualify for Medicaid coverage under HUSKY C (this includes

Medicaid for Employees with Disabilities (MED-Connect), if working). Income and asset limits apply.

4. **HUSKY D**: Connecticut residents who are ages 19-64 without dependent children and who: (1) do not qualify for HUSKY A; (2) do not receive Medicare; and (3) are not pregnant, may qualify for HUSKY D (also known as Medicaid for the Lowest-Income populations).
5. **HUSKY Health Program**: The HUSKY A, HUSKY B, HUSKY C, HUSKY D and HUSKY Limited Benefit programs, collectively.
6. **HUSKY Limited Benefit Program or HUSKY, LBP**: Connecticut's implementation of limited health insurance coverage under Medicaid for individuals with tuberculosis or for family planning purposes and such coverage is substantially less than the full Medicaid coverage.
7. **Medically Necessary or Medical Necessity**: (as defined in Connecticut General Statutes § 17b-259b) Those health services required to prevent, identify, diagnose, treat, rehabilitate or ameliorate an individual's medical condition, including mental illness, or its effects, in order to attain or maintain the individual's achievable health and independent functioning provided such services are: (1) Consistent with generally-accepted standards of medical practice that are defined as standards that are based on (A) credible scientific evidence published in peer-reviewed medical literature that is generally recognized by the relevant medical community, (B)recommendations of a physician-specialty society, (C) the views of physicians practicing in relevant clinical areas, and (D) any other relevant factors; (2) clinically appropriate in terms of type, frequency, timing, site, extent and duration and considered effective for the individual's illness, injury or disease; (3) not primarily for the convenience of the individual, the individual's health care provider or other health care providers; (4) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the individual's illness, injury or disease; and (5) based on an assessment of the individual and his or her medical condition.
8. **Prior Authorization**: A process for approving covered services prior to the delivery of the service or initiation of the plan of care based on a determination by CHNCT as to whether the requested service is medically necessary.

ADDITIONAL RESOURCES AND REFERENCES:

- Angelucci E, Benz EJ. Hematopoietic stem cell transplantation and other curative therapies for transfusion-dependent thalassemia. In *UpToDate.* Negrin RS, Chao NJ, Tirnauer JS (Eds), Wolters Kluwer. Updated December 3, 2024. Accessed on March 4, 2025
- Benz EJ, Angelucci E. Diagnosis of thalassemia (adults and children). In *UpToDate.* Vichinsky EP, Tirnauer JS (Eds), Wolters Kluwer. Updated November 21, 2024. Accessed on February 25, 2025.
- 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. doi:10.1016/S0140-6736(24)01884-1
- 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. doi:10.1056/NEJMoa2113206
- ZYNTEGLO [prescribing information], Somerville, MA; bluebird bio, Inc.; August 2022.

PUBLICATION HISTORY

Status	Date	Action Taken
Original publication	February 2025	Approved at the CHNCT Medical Reviewer meeting on March 12, 2025. Approved by the CHNCT Clinical Quality Subcommittee on March 17, 2025. Approved by DSS on April 3, 2025

Please note that authorization is based on medical necessity at the time the authorization is issued and is not a guarantee of payment. Payment is based on the individual having active coverage, benefits and policies in effect at the time of service.

To determine if a service or procedure requires prior authorization, CMAP Providers may refer to the Benefit Grid summaries on www.ct.gov/husky by clicking on *For Providers* followed by *Benefit Grids* under the *Medical Management* sub-menu. For a definitive list of benefits and service limitations, CMAP providers may access the CMAP provider fee schedules and regulations at www.ctdssmap.com.