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MEDICAL POLICY – 5.01.42

Gene Therapies for Thalassemia

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Effective Date:	May 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Apr. 21, 2025	None
Replaces:	N/A	

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HISTORY

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Introduction

Beta (β) thalassemia is an inherited blood condition where the body makes less hemoglobin. Hemoglobin is a protein in red blood cells. It carries oxygen to all of the body's cells. β-thalassemia can cause tiredness, slow growth rates, abnormal bone changes, weak bones, abnormal growths on the spinal cord, and heart problems. Common treatments for β-thalassemia include blood transfusions, removing extra iron from the body with drugs, and blood stem cell transplants from a donor. Another way to treat β-thalassemia is with gene therapy. Gene therapy uses a person's own blood stem cells to help change the abnormal gene that causes β-thalassemia to get worse. The altered gene is mixed with a drug and put back in the body through a vein (an infusion). The goal of gene therapy for β-thalassemia is for the person's body to make enough hemoglobin so that blood transfusions are no longer needed. This policy describes when gene therapies may be considered medically necessary for people who have β-thalassemia and need regular red blood cell transfusions.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity

Casgevy (exagamglogene autotemcel)	**Casgevy (exagamglogene autotemcel) is considered medically necessary for individuals with transfusion-dependent β-thalassemia when all the following criteria are met:**
	• The individual is aged 12 to 35 years
	• Documented diagnosis of β-thalassemia by globin gene testing
	• Require regular peripheral blood transfusions to maintain target hemoglobin levels
	• Documented history of receiving transfusions of at least 100 ml per kilogram of body weight of packed red cells per year or who had disease that had been managed under standard thalassemia guidelines with at least 8 transfusions per year in the previous 2 years at the time of treatment decision
	• Karnofsky performance status of at least 80 for adults (aged 16 years or older) or a Lansky performance status of at least 80 for adolescents (less than 16 years of age)
	• Negative serologic test for HIV infection (as per US Food and Drug Administration prescribing label, apheresis material from individuals with a positive test for HIV will not be accepted for exagamglogene autotemcel manufacturing)
	• The individual does not have:
	  ○ Availability of human leukocyte antigen-identical or human leukocyte antigen-matched donor
	  ○ T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec or other evidence of severe iron overload in the opinion of treating physician.
	  ○ Advanced liver disease (meets any one of the following):
	  ▪ Persistent aspartate transaminase, alanine transaminase, or direct bilirubin value greater than 3 times the upper limit of normal
	  ▪ Baseline prothrombin time or partial thromboplastin time greater than 1.5 times the upper limit of normal
	  ▪ Magnetic resonance imaging of the liver demonstrating clear evidence of cirrhosis

Drug	Medical Necessity
	▪ Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis ○ Baseline estimated glomerular filtration rate less than 70 mL/min/1.73 m^2 ○ History of receiving prior gene therapy or allogenic hematopoietic stem cell transplant ○ Any prior or current malignancy (except for non-melanoma skin cancers) ○ Contraindication to the use of plerixafor, busulfan, or any other medicinal products required during myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients • The individual is clinically stable and eligible to undergo a hematopoietic stem cell transplant
Zynteglo (betibeglogene autotemcel)	**Zynteglo (betibeglogene autotemcel) is considered medically necessary for individuals with transfusion-dependent β-thalassemia when all the following criteria are met:** • The individual is aged 50 years or younger • Documented diagnosis of β-thalassemia by globin gene testing • Require regular peripheral blood transfusions to maintain target hemoglobin levels • Documented history of receiving transfusions of at least 100 ml per kilogram of body weight of packed red cells per year or who had disease that had been managed under standard thalassemia guidelines with at least 8 transfusions per year in the previous 2 years at the time of treatment decision • Karnofsky performance status of at least 80 for adults (aged 16 years or older) or a Lansky performance status of at least 80 for adolescents (less than 16 years of age) • Negative serologic test for HIV infection (as per US Food and Drug Administration prescribing label, apheresis material from individuals with a positive test for HIV will not be accepted for betibeglogene autotemcel manufacturing) • The individual does not have: ○ Availability of human leukocyte antigen-identical or human leukocyte antigen-matched donor

Drug	Medical Necessity
	○ T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec or other evidence of severe iron overload in the opinion of treating physician ○ Advanced liver disease (meets any one of the following): ▪ Persistent aspartate transaminase, alanine transaminase, or direct bilirubin value greater than 3 times the upper limit of normal ▪ Baseline prothrombin time or partial thromboplastin time greater than 1.5 times the upper limit of normal ▪ Magnetic resonance imaging of the liver demonstrating clear evidence of cirrhosis ▪ Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis ○ Baseline estimated glomerular filtration rate less than 70 mL/min/1.73 m^2 ○ History of receiving prior gene therapy or allogenic hematopoietic stem cell transplant ○ Any prior or current malignancy (with the exception of adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin) or myeloproliferative or significant immunodeficiency disorder ○ Any immediate family member (i.e., parent or siblings) with a known Familial Cancer Syndrome (including but not limited to hereditary breast and ovarian cancer syndrome, hereditary nonpolyposis colorectal cancer syndrome and familial adenomatous polyposis) ○ Active, uncontrolled HCV or HBV infection ○ Contraindication to the use of granulocyte colony stimulating factor (G-CSF), plerixafor, busulfan, or any other medicinal products required during myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients ○ A white blood cell count less than 3 X 10^9/L, and/or platelet count less than 100 X 10^9/L not related to hypersplenism ○ An uncorrected bleeding disorder

Drug	Medical Necessity
	• Individuals aged less than 5 years must weigh a minimum of 6 kg • The individual is clinically stable and eligible to undergo a hematopoietic stem cell transplant

Drug	Investigational
Casgevy (exagamglogene autotemcel), Zynteglo (betibeglogene autotemcel)	**All other uses of Casgevy (exagamglogene autotemcel) and Zynteglo (betibeglogene autotemcel) for conditions not outlined in this policy are considered investigational.** **Repeat treatment of Casgevy (exagamglogene autotemcel) and Zynteglo (betibeglogene autotemcel) is considered investigational.** **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for Casgevy (exagamglogene autotemcel) or Zynteglo (betibeglogene autotemcel) may be approved up to 12 months.** **All other reviews for Casgevy (exagamglogene autotemcel) or Zynteglo (betibeglogene autotemcel) may be approved as a one-time infusion.**
Re-authorization criteria	**Repeat treatment of Casgevy (exagamglogene autotemcel) or Zynteglo (betibeglogene autotemcel) is considered investigational.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following if applicable:

Documentation Requirements

1. Documented diagnosis of β-thalassemia by globin gene testing.
2. Require regular peripheral blood transfusions to maintain target hemoglobin levels.
3. Documented history of receiving transfusions of ≥100 ml per kilogram of body weight of packed red cells per year or who had disease that had been managed under standard thalassemia guidelines with ≥8 transfusions per year in the previous 2 years at the time of treatment decision.
4. Karnofsky performance status of ≥80 for adults (≥16 years of age) or a Lansky performance status of ≥80 for adolescents (<16 years of age).
5. Negative serologic test for HIV infection (as per US FDA prescribing label, apheresis material from individuals with a positive test for HIV will not be accepted for manufacturing).
6. Individual does not have:
    a. Availability of human leukocyte antigen-identical or human leukocyte antigen-matched donor.
    b. T2*-weighted magnetic resonance imaging measurement of myocardial iron of less than 10 msec or other evidence of severe iron overload in the opinion of treating physician.
    c. Advanced liver disease (meets any one of the following):
        i. Persistent aspartate transaminase, alanine transaminase, or direct bilirubin value greater than 3 times the upper limit of normal.
        ii. Baseline prothrombin time or partial thromboplastin time greater than 1.5 times the upper limit of normal.
        iii. Magnetic resonance imaging of the liver demonstrating clear evidence of cirrhosis.
        iv. Liver biopsy demonstrating cirrhosis, any evidence of bridging fibrosis, or active hepatitis.
    d. Baseline estimated glomerular filtration rate less than 70 mL/min/1.73 m^2.
    e. History of receiving prior gene therapy or allogenic hematopoietic stem cell transplant.
    f. Any prior or current malignancy (with the exception of adequately treated cone biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin) or myeloproliferative or significant immunodeficiency disorder.
    g. Any immediate family member (i.e., parent or siblings) with a known Familial Cancer Syndrome (including but not limited to hereditary breast and ovarian cancer syndrome, hereditary nonpolyposis colorectal cancer syndrome and familial adenomatous polyposis).
    h. Active, uncontrolled HCV or HBV infection.
    i. Contraindication to the use of granulocyte colony stimulating factor (G-CSF), plerixafor, busulfan, or any other medicinal products required during myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients.
    j. A white blood cell count less than 3 X 10^9/L, and/or platelet count less than 100 X 10^9/L not related to hypersplenism.
    k. An uncorrected bleeding disorder

Documentation Requirements
l. Any prior or current malignancy 7. Individuals <5 years of age must weight a minimum of 6 kg 8. Individual is clinically stable and eligible to undergo a hematopoietic stem cell transplant

Coding

Code	Description
HCPCS	
J3392	Injection, exagamglogene autotemcel, per treatment (Casgevy) (new code effective 01/01/25)
J3393	Injection, betibeglogene autotemcel, per treatment (Zynteglo) (new code effective 07/01/24)
J3590	Unclassified Biologics (use to report: Casgevy)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Recommended Dose

The minimum recommended dose is 5.0 X 106 CD34+ cells/kg of body weight.

Dosing Limits

1 injection per lifetime

Other Considerations

- Prophylaxis for hepatic veno-occlusive disease is recommended. Prophylaxis for seizures should be considered.

- Monitor platelet counts until platelet engraftment and recovery are achieved. Individuals should be monitored for thrombocytopenia and bleeding.
- Monitor absolute neutrophil counts after betibeglogene autotemcel infusion. If neutrophil engraftment does not occur administer rescue cells.
- Monitor individuals at least annually for hematologic malignancies for at least 15 years after betibeglogene autotemcel infusion.
- Individuals should not take prophylactic anti-retroviral medications or hydroxyurea for at least 1 month prior to mobilization or the expected duration for elimination of the medications, and until all cycles of apheresis are completed as anti-retroviral medications may interfere with manufacturing of the apheresed cells.
- Iron chelators should be discontinued at least 7 days prior to initiation of conditioning. After betibeglogene autotemcel infusion, avoid use of these iron chelators for 6 months. If iron chelation is needed, consider the administration of non-myelosuppressive iron chelators. Phlebotomy can be used in lieu of iron chelation, when appropriate.

Benefit Application

Casgevy (exagamglogene autotemcel) and Zynteglo (betibeglogene autotemcel) are managed through the medical benefit.

Evidence Review

Description

β-thalassemia is a genetic hemoglobinopathy that results from defects in β-globin synthesis leading to reduced synthesis or absence of β-globin chains causing impaired production of hemoglobin. The clinical presentation is that of anemia which requires transfusion and multiple downstream sequelae from iron overload. It is estimated that at least 1000 people in the United States have transfusion-dependent β-thalassemia. Betibeglogene autotemcel contains autologous CD34+ hematopoietic stem cells in which functional copies of a modified form of the β-globin gene (βA-T87Q-globin gene) have been added. Once the hematopoietic stem cells reengineered with $\beta^{A\text{-}T87Q}$ are infused, they engraft in the bone marrow and differentiate to

produce red blood cells containing $\beta^{A\text{-}T87Q}$ gene that will produce HbA^{T87Q} protein (functional gene therapy-derived hemoglobin) at levels that may eliminate or significantly reduce the need for transfusions.

Background

β-Thalassemia

It is an inherited blood disorder that occurs as a result of a genetic variant in the HBB gene that codes for the production of β-globin chains. As a result, there is reduced synthesis or absence of β-globin chains leading to impaired production of hemoglobin. The clinical presentation is that of anemia which requires iron supplementation and multiple downstream sequelae from the disease. These sequelae include growth retardation, skeletal changes (particularly in the face and long bones of the legs), osteoporosis, leg ulcers, and development of extramedullary masses. High output heart failure from anemia is also common without treatment. Without transfusion therapy, such individuals die within the first few years of life, primarily from heart failure or infection.[1]

Life expectancy of individuals with transfusion-dependent β-thalassemia is much lower than population norms. From 2011 to 2021 the median age of death for a person in the US with transfusion-dependent β-thalassemia was 37.[2] Additionally, individuals with transfusion-dependent β-thalassemia report decreased quality of life due to the impact on physical and mental health.[3,4]

All humans have 2 copies of the HBB gene and each copy produces the β-globin protein. Different types of β-thalassemia categorized by genotype are summarized in Table 1. When only 1 HBB gene is affected, the phenotype is less severe and individuals are generally asymptomatic due to compensation from the other normal gene. These individuals are called β-thalassemia minor or carrier. However, if both copies of HBB gene are affected there is a quantitative reduction or absence of β-globin protein. Phenotypes that manifest as a reduction in β-globin chains are referred to as "β-thalassemia intermedia" and phenotypes that manifest as absence in β-globin chains are called "β-thalassemia major".[5]

More recently, individuals have been classified according to their transfusion status (i.e., transfusion-dependent β-thalassemia or non-transfusion-dependent β-thalassemia). For this evidence review, we will focus on transfusion-dependent β-thalassemia individuals which generally includes "β-thalassemia major" but occasionally may include individuals with "β-thalassemia intermedia". Clinical studies reviewed define "transfusion dependence" as history of

at least 100 mL/kg/year of peripheral red blood cells or ≥8 transfusions of peripheral red blood cells per year for the prior 2 years. "Transfusion independence" was defined as a weighted average hemoglobin (Hb) of at least 9 g/dL without any transfusions for a continuous period of at least 12 months at any time during the study after infusion of betibeglogene autotemcel.

Table 1. Different Types of β-Thalassemia[5,6,7]

Type	Genotype	Description
β-thalassemia major (generally transfusion dependent)	β^0/β^0 or β^0/β^+	• Presents within the first 2 years of life with severe microcytic anemia (typical hemoglobin 3 to 4 g/dL), mild jaundice, and hepatosplenomegaly • Requires regular red blood cell transfusions and other medical treatments
Thalassemia intermedia	β^+/β^+	• Presents at a later age with similar, but milder, clinical signs and symptoms of thalassemia • Moderately severe anemia; some may need regular blood transfusion
Thalassemia minor	β/β^0 or β/β^+	• Also called "β-thalassemia carrier" or "β-thalassemia trait" • Usually clinically asymptomatic but may have a mild anemia • Generally do not require any treatment

β^0 refers to no beta globin production; β^+ refers to decreased beta globin production.

Epidemiology

β-thalassemia is one of the most common monogenic disorders, but its incidence varies geographically. Higher incidence and prevalence have been reported among individuals from Mediterranean, Africa, the Middle East, and Southeast Asia. While its occurrence is rare in United States, the pattern shows an increasing trend with migration and is expected to increase in the future. According to Bluebird Bio, approximately 1500 people in the United States currently live with transfusion-dependent β-thalassemia.[8]

Diagnosis

The diagnostic pathway for symptomatic thalassemia syndromes (thalassemia major and thalassemia intermedia) in a neonate, infant, or child begins with either recognition of symptoms

(anemia, evidence of hemolysis and extramedullary hematopoiesis such as jaundice, skeletal abnormalities, and/or splenomegaly) or may be suspected based on a known family history. Initial laboratory testing includes a complete blood count, review of the blood smear, and iron studies. DNA-based genotyping of globin gene can be done relatively inexpensively, is required for precise diagnosis, and is especially important in carrier detection, prenatal testing, and genetic counseling.[5]

Treatment

The current standard of care for transfusion-dependent β-thalassemia includes blood transfusion, iron chelation therapies, and allogenic hematopoietic stem cell transplant.

As per the 2014 Thalassemia International Federation guidelines, transfusion is indicated when hemoglobin levels are less than 7 g/dL on 2 different occasions more than 2 weeks apart, or when hemoglobin levels are greater than 7 g/dL but there are co-occurring complications such as facial changes, poor growth, fractures, or clinically significant extramedullary hematopoiesis. The goal of treatment is to maintain a hemoglobin level of 9 to 10.5 g/dL, which has been shown to promote normal growth, suppress bone marrow activity, and minimize iron accumulation.[9,10] Transfusions are typically required every 2 to 5 weeks to reach this goal but can vary for individuals such as those with heart failure who may require higher target hemoglobin levels.[11,] Risks of repeated blood transfusions include transfusion reactions, allergic reactions, hemolytic anemia, transfusion-related acute lung injury, and transfusion-related graft versus host disease and alloimmunization.[12] In the event of alloimmunization, it becomes difficult to find a matched blood and also increases the likelihood of delayed transfusion reactions. However, the main complication from frequent blood transfusions is iron overload.

Iron overload as a result of frequent transfusion results in iron accumulation in the heart, liver, and pituitary gland and can lead to heart failure, cirrhosis, hepatocellular carcinoma, hypothyroidism, hypoparathyroidism, hypogonadism, diabetes, and growth failure.[13] Primary treatment for iron overload is chelation therapy (desferrioxamine, deferasirox, deferiprone) and is typically initiated after 10 to 20 transfusions or when the serum ferritin level rises above 1000 mcg/L.14, Chelation therapy is associated with side effects such as hearing problems, bone growth retardation and local reactions, gastrointestinal symptoms, arthralgia, and neutropenia. Another limitation of chelation therapy is lack of adherence when infused therapies are used as compared to higher adherence for individuals taking oral therapy.[15]

Hematopoietic stem cell transplant is the only curative treatment with cure rates ranging from 80% to 90% in children who receive human leukocyte antigen-identical sibling transplant.[16] Cure

rates in adults are lower with a reported range of 65% to 70%.[17] While the cure rates are high, the main limiting factor for hematopoietic stem cell transplant is lack of a compatible donor. Fewer than 25% of individuals have compatible related or unrelated donors, and transplants with mismatched donors or unrelated umbilical cord blood have a lower success rate.[18] Complications from hematopoietic stem cell transplant include mucositis, infection, graft failure, and graft versus host disease. If available, hematopoietic stem cell transplant should be offered to individuals early in the disease course, prior to the onset of iron overload.[14]

There are no randomized trials comparing hematopoietic stem cell transplant with medical therapy for transfusion-dependent thalassemia.[19] Only a 2017 retrospective case-control study has been published, showing no statistically different overall survival with transplantation versus conventional medical therapy (e.g., transfusions and iron chelation).[17] The Center for International Blood and Marrow Transplant Research reported the results of a retrospective cohort of 1110 individuals with β-thalassemia who received a hematopoietic stem cell transplant between 2000 and 2016. The median age at transplantation was 6 years (range: 1 to 25 years), 61% received transplants with grafts from HLA-matched related donors, 7% from HLA-mismatched related donors, 23% from HLA-matched unrelated donors, and 9% from HLA-mismatched unrelated donors. The results are summarized in **Table 2**.

Table 2. Outcomes of Retrospective Cohort of Individuals Who Received Hematopoietic Stem Cell Transplant for β-Thalassemia

Outcome	Matched Sibling	Matched Unrelated	Mismatched Relative	Mismatched Unrelated
5-year survival	89% (n=677)	87% (n=252)	73% (n=78)	83% (n=103)
Graft failure	8.6% (n=677)	5.2% (n=252)	21.8% (n=78)	10.7% (n=103)
Grade 2-4 acute GVHD	11.9% (n=674)	21.5% (n=251)	35.1% (n=77)	19.8% (n=101)
Chronic GVHD	8.3% (n=627)	8.4% (n=249)	20% (n=70)	23.8% (n=101)

[a]Matched relative representative of matched sibling in this study.
GVHD: graft-versus-host disease

Zynteglo (betibeglogene autotemcel)

For individuals with transfusion-dependent β-thalassemia who receive betibeglogene autotemcel, the evidence includes 2 single-arm studies: HGB-207 (Northstar-2) and HGB-212 (Northstar-3). The Northstar-2 trial enrolled non- $\beta^0\beta^0$ genotype (less severe phenotype) while Northstar-3 trial enrolled β-thalassemia individuals with either a β^0 or β^+ IVS1 110 (G>A) variant (severe phenotype) at both alleles of the HBB gene. Relevant outcomes are change in disease status, quality of life, hospitalizations, medication use, treatment-related morbidity and treatment-related mortality. The 2 open-label, phase III, single-arm studies included a total of 41 individuals who received a single intravenous infusion of betibeglogene autotemcel. Of the 41 participants, 36 participants in whom transfusion independence was evaluable were included in the efficacy analysis. Transfusion independence was achieved in 89% (95% CI, 74% to 97%) of study participants. Limitations include a small sample size and limited duration of follow-up. There is uncertainty regarding the durability of effect over a longer time period. Long-term follow-up (>15 years) is required to establish precision around durability of the treatment effect. The small sample size creates uncertainty around the estimates of some of the individual-important outcomes, particularly adverse events. Some serious harms are likely rare occurrences and, as such, may not be observed in small trials. While most of the serious adverse events were attributable to known risks associated with myeloablative conditioning, uncertainty still remains about the degree of risk with betibeglogene autotemcel infusion in real-world practice. Insertional oncogenesis has been identified as a potential risk with transgene integration. There has been no evidence of insertional oncogenesis and no malignancies in the trials of betibeglogene autotemcel. However, cases of myelodysplastic syndrome and acute myeloid leukemia have been reported in gene therapy trials that use a lentiviral vector to treat other conditions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Ongoing trials that might influence this review are listed in **Table 3**.

Table 3. Summary of Ongoing and Unpublished Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing – betibeglogene autotemcel			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02633943[a]	Long-term Follow-up of Subjects With Transfusion-Dependent β-Thalassemia Treated With Ex Vivo Gene Therapy	66	November 2035
Ongoing – exagamglogene autotemcel			
NCT05477563	Evaluation of Efficacy and Safety of a Single Dose of CTX001 in Participants With Transfusion-Dependent β-Thalassemia and Severe Sickle Cell Disease	26	February 2025
NCT05356195	Evaluation of Safety and Efficacy of CTX001 in Pediatric Participants With Transfusion-Dependent β-Thalassemia	15	May 2026
NCT04208529	A Long-term Follow-up Study in Participants Who Received CTX001	160	September 2039
NCT03655678	A Safety and Efficacy Study Evaluating CTX001 in Subjects With Transfusion-Dependent β-Thalassemia	59	December 2025

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Institute for Clinical and Economic Review

The Institute for Clinical and Economic Review published a final report on comparative effectiveness and value of betibeglogene autotemcel for beta thalassemia on July 19, 2022.[24] The Report concluded that betibeglogene autotemcel to be incremental or better with moderate certainty of a small or substantial net health benefit ("B+") versus standard of care.

National Institute for Health and Care Excellence

On September 11, 2024, the NICE issued technology appraisal guidance on exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia in people 12 years and over. Exagamglogene autotemcel is recommended with managed access as an option for treating transfusion-dependent beta-thalassaemia in people 12 years and over:

- when a HSCT is suitable, but a human leukocyte antigen-matched related hematopoietic stem cell donor is not available
- only if the conditions in the managed access agreement for exa-cel are followed.

Cooley's Anemia Foundation

The Children's Hospital & Research Center Oakland published the standards of care guidelines for thalassemia in 2012.[25,] These guidelines have not been updated since they were published.

2023 Updates

Reviewed prescribing information of Zynteglo. Updated Zynteglo criteria to require that the individual does not have an uncorrected bleeding disorder, any prior or current malignancy, or history of advanced liver disease. Also, individuals must be 50 years of age or younger and <5 years must weigh a minimum of 6 kg. Lastly, the individual must be clinically stable and eligible to undergo a hematopoietic stem cell transplant.

2024 Updates

Reviewed prescribing information of Zynteglo. Added coverage criteria for Casgevy (exagamglogene autotemcel).

2025 Updates

Reviewed prescribing information for Casgevy and Zynteglo. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing

information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

References

1. Borgna-Pignatti C. The life of patients with thalassemia major. Haematologica. Mar 2010; 95(3): 345-8. PMID 20207838
2. Chieco P and Butler C. 2021 CAF Information - The Cooleys Anemia Foundation. Published January 21st, 2022; Available at 2021 CAF Information - The Cooley's Anemia Foundation (thalassemia.org). Accessed April 7, 2025.
3. Arian M, Mirmohammadkhani M, Ghorbani R, et al. Health-related quality of life (HRQoL) in beta-thalassemia major (-TM) patients assessed by 36-item short form health survey (SF-36): a meta-analysis. Qual Life Res. Feb 2019; 28(2): 321-334. PMID 30194626
4. Vitrano A, Calvaruso G, Lai E, et al. The era of comparable life expectancy between thalassaemia major and intermedia: Is it time to revisit the major-intermedia dichotomy?. Br J Haematol. Jan 2017; 176(1): 124-130. PMID 27748513
5. Langer AL. Beta-Thalassemia. 2000 Sep 28 [Updated 2023 Jul 20]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1426/
6. Origa R. Beta-Thalassemia. 2000 Sep 28 [Updated 2021 Feb 4]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: **https://www.ncbi.nlm.nih.gov/books/NBK1426/**. Accessed April 7, 2025.
7. Galanello R, Origa R. Beta-thalassemia. Orphanet J Rare Dis. May 21 2010; 5: 11. PMID 20492708
8. Chonat S, Quinn CT. Current Standards of Care and Long Term Outcomes for Thalassemia and Sickle Cell Disease. Adv Exp Med Biol. 2017; 1013: 59-87. PMID 29127677
9. beta-thalassemia (beta-thal). Bluebird Bio. Our Focus: Transfusion-Dependent Beta-Thalassemia (TDT) | bluebird bio Accessed April 7, 2025.
10. Cazzola M, Borgna-Pignatti C, Locatelli F, et al. A moderate transfusion regimen may reduce iron loading in beta-thalassemia major without producing excessive expansion of erythropoiesis. Transfusion. Feb 1997; 37(2): 135-40. PMID 9051086
11. Cazzola M, Locatelli F, De Stefano P. Deferoxamine in thalassemia major. N Engl J Med. Jan 26 1995; 332(4): 271-2; author reply 272-3. PMID 7808503
12. Kremastinos DT, Farmakis D, Aessopos A, et al. Beta-thalassemia cardiomyopathy: history, present considerations, and future perspectives. Circ Heart Fail. May 2010; 3(3): 451-8. PMID 20484195
13. Thompson AA, Cunningham MJ, Singer ST, et al. Red cell alloimmunization in a diverse population of transfused patients with thalassaemia. Br J Haematol. Apr 2011; 153(1): 121-8. PMID 21323889
14. Olivieri NF, Liu PP, Sher GD, et al. Brief report: combined liver and heart transplantation for end-stage iron-induced organ failure in an adult with homozygous beta-thalassemia. N Engl J Med. Apr 21 1994; 330(16): 1125-7. PMID 8133854
15. Cappellini MD, Cohen A, Porter J, et al., editors. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) [Internet]. 3rd edition. Nicosia (CY): Thalassaemia International Federation; 2014. Available from: **https://www.ncbi.nlm.nih.gov/books/NBK269382/**. Accessed April 7, 2025.
16. Trachtenberg F, Vichinsky E, Haines D, et al. Iron chelation adherence to deferoxamine and deferasirox in thalassemia. Am J Hematol. May 2011; 86(5): 433-6. PMID 21523808

17. Baronciani D, Angelucci E, Potschger U, et al. Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000-2010. Bone Marrow Transplant. Apr 2016; 51(4): 536-41. PMID 26752139

18. Caocci G, Orofino MG, Vacca A, et al. Long-term survival of beta thalassemia major patients treated with hematopoietic stem cell transplantation compared with survival with conventional treatment. Am J Hematol. Dec 2017; 92(12): 1303-1310. PMID 28850704

19. Angelucci E, Matthes-Martin S, Baronciani D, et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. Haematologica. May 2014; 99(5): 811-20. PMID 24790059

20. Sharma A, Jagannath VA, Puri L. Hematopoietic stem cell transplantation for people with -thalassaemia. Cochrane Database Syst Rev. Apr 21 2021; 4: CD008708. PMID 33880750

21. Thompson AA, Walters MC, Kwiatkowski J, et al. Gene Therapy in Patients with Transfusion-Dependent -Thalassemia. N Engl J Med. Apr 19 2018; 378(16): 1479-1493. PMID 29669226

22. Magrin E, Semeraro M, Hebert N, et al. Long-term outcomes of lentiviral gene therapy for the -hemoglobinopathies: the HGB-205 trial. Nat Med. Jan 2022; 28(1): 81-88. PMID 35075288

23. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene Autotemcel Gene Therapy for Non- 0 / 0 Genotype - Thalassemia. N Engl J Med. Feb 03 2022; 386(5): 415-427. PMID 34891223

24. Prescribing Label: ZYNTEGLO (betibeglogene autotemcel) suspension for intravenous infusion. Initial US Approval: 2022. Available at **https://www.fda.gov/media/160991/download**. Accessed April 7, 2025.

25. Institute for Clinical and Evidence Review. Betibeglogene Autotemcel for Beta Thalassemia: Effectiveness and Value (Final Evidence Report July 19, 2022). Available at **https://icer.org/beta-thalassemia-2022/**. Accessed April 7, 2025.

26. Standards of Care Guidelines for Thalassemia- 2012. Published by Childrens Hospital & Research Center Oakland. Available at **https://thalassemia.com/documents/SOCGuidelines2012.pdf**. Accessed April 7, 2025.

27. 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. Nov 30 2024; 404(10468): 2175-2186. PMID 39527960

28. Prescribing Label: Casgevy (exagamglogene autotemcel) suspension for intravenous infusion. Available at https://www.casgevyhcp.com/sites/default/files/uspi-ppi_exagamglogene_autotemcel.pdf. Accessed April 7, 2025.

29. Locatelli F, Lang P, Wall D, et al. Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia. N Engl J Med. May 09 2024; 390(18): 1663-1676. PMID 38657265

30. National Institute for Health and Care Excellence. Technology appraisal guidance TA1003. Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia in people 12 years and over. Available at https://www.nice.org.uk/guidance/ta1003. Accessed April 7, 2025.

History

Date	Comments
12/01/22	New policy, approved November 8, 2022. Policy created with literature review through August 17, 2022. The use of betibeglogene autotemcel is considered medically

Date	Comments
	necessary for individuals with transfusion dependent beta thalassemia when certain conditions are met. Added HCPC code J3590 to report Zynteglo.
08/01/23	Annual Review, approved July 10, 2023. No changes to the policy statements.
12/01/23	Interim Review, approved November 14, 2023, effective for dates of service on or after March 7, 2024, following 90-day provider notification. Updated Zynteglo criteria to require that the individual does not have an uncorrected bleeding disorder or history of advanced liver disease. Also, individuals must be 50 years of age or younger and <5 years must weigh a minimum of 6 kg. Lastly, the individual must be clinically stable and eligible to undergo a hematopoietic stem cell transplant.
06/01/24	Annual Review, approved May 14, 2024. Added coverage criteria for Casgevy (exagamglogene autotemcel).
07/01/24	Coding update. Added HCPCS code J3393.
01/01/25	Coding update. Added new HCPCS code J3392.
05/01/25	Annual Review, approved April 21, 2025. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.