Molina Clinical Policy
Casgevy (exagamglogene autotemcel) for Beta Thalassemia: Policy No. 449

Last Approval: 02/12/2025
Next Review Due By: February 2026

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

This policy reviews Casgevy for the treatment of beta thalassemia. Thalassemia's are a heterogeneous group of autosomal recessive genetic disorders characterized by decreased or absent synthesis of globin chains leading to anemia and microcytosis. Clinically, there are two major forms: α-thalassemia and β-thalassemia.

Beta (β) thalassemia is a hereditary anemia caused by mutations in the β-globin (HBB) gene resulting in impaired hemoglobin production. When β-globin is markedly reduced or absent, red blood cell production is ineffective and red blood cell destruction occurs leading to significant anemia. Historically, beta thalassemia has been classified into major or minor forms. Individuals with β-thalassemia minor have a mutation in one HBB gene, while individuals with the intermediate and major forms have mutations in both HBB genes:

Minor (trait or carrier)	Mild Microcytic
Intermedia (non-transfusion-dependent)	Moderate Microcytic
Major (transfusion-dependent)	Severe microcytic with target cells (typical Hb 3 to 4 g/dL)

Mutation severity is related to the amount of anemia they cause and are denoted by the symbols, β+ and β^0. Anemia due to β+ mutations ranges from mild to severe depending on the nature of the second mutation. An allele with a β^0 mutation has no detectable β-globin production (Benz and Angelucci 2022) and the genotype β^0 β^0 would result in severe anemia.

The Thalassemia International Federation (TIF) guidelines (2021) classify β-thalassemia phenotypically into two main groups based on clinical severity and transfusion requirements regardless of the underlying genotype: transfusion-dependent thalassemia and non-transfusion dependent thalassemia (TIF 2021).

Transfusion-dependent β-thalassemia (TDT; previously thalassemia major) is a rare, severe, genetic disease characterized by reduced or absent β-globin protein in adult hemoglobin due to mutations in the HBB gene. The anemia is so profound that people with TDT require life-long red-cell transfusions and have impaired quality of life. TDT can also cause ineffective erythropoiesis in pediatric patients, which can lead to bone deformities and growth retardation (National Organization for Rare Disorders, 2021; Benz et al. 2022). The clinical management of TDT focuses primarily on anemia-related symptoms and consists of lifelong, regular (usually every 2 to 5 weeks) blood transfusions to maintain a pre-transfusion hemoglobin level above 9 g/dL and iron chelation therapy to remove excess iron introduced with transfusions. Transfusion-induced iron overload causes widespread organ damage, most notably affecting the cardiac, hepatic, and endocrine system and is the predominant cause of morbidity and mortality. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only permanent curative option for TDT β-thalassemia patients, but this option is only available to those with a human leukocyte antigen (HLA) matched donor. Most with TDT do not have a suitable donor for HSCT. Gene therapy, which involves autologous

transplantation of genetically modified hematopoietic stem cells that corrects the anemia, is a novel therapeutic option recently approved by the FDA.

Exagamglogene autotemcel (Casgevy, CTX001) is a new, first in class gene-cell therapy for the treatment of transfusion dependent beta thalassemia. Casgevy gene-cell therapy modifies a patient's own CD34+ stem cells with the clustered regularly interspaced short palindromic repeats associated protein 9 (CRISPR/cas9) system to turn on fetal hemoglobin production. Enhanced expression of fetal hemoglobin increases the proportion of functional hemoglobin capable of oxygen transport.

This therapy is not only unique in that it is the first therapy to use CRISPR technology, but also in its target. Casgevy does not directly target or edit the beta globin gene mutation that causes beta thalassemia. Instead, Casgevy indirectly promotes the expression of fetal hemoglobin (HbF). Fetal hemoglobin is normally expressed until three months of age when a repressor appears in development that turns off fetal hemoglobin. After fetal hemoglobin is turned off, adult hemoglobin is produced.

In someone with beta thalassemia, it is at this transition from fetal to adult hemoglobin when signs and symptoms of anemia develop. Because fetal hemoglobin uses gamma globin instead of beta globin as a carrier of oxygen, the effects of the beta globin mutation are lessened. If a significant amount of fetal hemoglobin is expressed in adults, it could partially restore oxygen transport and reduce or eliminate anemia. Casgevy (exa-cel) promotes the expression of gamma globin by removing its natural repressor. Once gamma globin expression is restored, fetal hemoglobin is made. Real world evidence supports the clinical benefit of HbF once it reaches 20% or higher of total hemoglobin. In a nutshell, Casgevy turns back the clock on the developmental switch from HbF to adult hemoglobin by repressing, a repressor of HbF.

Note, the faulty beta globin gene and its expression are untouched and still produce some degree of hemoglobin with potential to sickle albeit at lower levels. Casgevy CRISPR/cas9 therapy is delivered to CD34+ stem cells via electroporation; viral vectors are not used.

FDA approval of Casgevy was based on interim data from the phase 1/2/3 CLIMB THAL-111 trial. The CLIMB -111 trial is an ongoing 2-year study of a single dose of Casgevy in patients with transfusion dependent beta thalassemia.

Side effects of Casgevy were similar to those that occur with autologous stem cell transplants. All significant adverse events resolved. Off-target genome editing is a risk and cannot be ruled out.

Administration of Casgevy involves harvesting the patients stem cells, and once outside the body, purifying and editing the patient's cells. Once enough edited cells are grown, the cells are shipped back to the treatment center in preparation for transfusion into the patient. The patient will then go through standard myeloablation procedures and remain in the hospital after receiving their edited cells while engraftment occurs.

RELATED POLICIES

MCP-420: Zynteglo (betibeglogene autotemcel) for Beta Thalassemia
MCP-447: Casgevy (exagamglogene autotemcel) for Sickle Cell Disease

COVERAGE POLICY

All Gene Therapy requests require Molina Medical Director review.

Casgevy (exa-cel **or** exagamglogene autotemcel**)** for the treatment of transfusion dependent beta thalassemia may be **considered medically necessary** when **ALL** the following clinical criteria are met (documentation required):

1. A diagnosis of transfusion dependent beta thalassemia (a-c):
    a. Genetic testing confirming bi-allelic pathogenic mutations in the beta globin gene consistent with beta thalassemia (documentation required)

b. No mutations consistent with alpha thalassemia (mutations, deletions or duplications)
c. Phenotype consistent with transfusion dependent beta thalassemia: History of at least 100 mL/kg/year or ≥10 units/year of packed RBC transfusions in the past 2 years

2. Clinical documentation and recent relevant evaluation, labs, and workup establishing eligibility for autologous stem cell transplant including the Eastern Cooperative Oncology Group Performance Status of 0 or 1 (ambulatory and able to carry out work of a light or sedentary nature); OR Karnofsky or Lansky performance status of at least 80%

3. Member does not have an HLA matched related donor available

4. Member has not had previous hematopoietic stem cell transplant

5. Member does not have significant active infections or cytopenias (white blood cell count < 3 $x10^9$/L or platelet count < 50 x 10^9/L

6. Member does not have a baseline hemoglobin F concentration >15%

7. Member has adequate and stable renal, liver, lung, and cardiac function as evidenced by recent evaluation and laboratory workup (a-f):
   a. Estimated glomerular filtration rate ≥ 60ml/min/1.73 m^2
   b. Liver function tests < 3 x ULN; no history of cirrhosis, bridging fibrosis or severe iron deposition in the liver
   c. Direct bilirubin < 2.5 x the Upper Limit of Normal (ULN)
   d. Prothrombin time (INR – International normalized ratio) ≤ 1.5 x ULN
   e. Carbon monoxide diffusion capacity of the lung (DLCO) ≥ 50% (corrected for Hb and or alveolar volume)
   f. Left ventricular ejection fraction ≥ 45% and no history of severely elevated iron in the heart

8. Member has not received a gene therapy, or is not being considered for other gene therapies, or investigational cellular therapy for transfusion dependent beta thalassemia

9. Member is 12 years of age or greater, but less than or equal to 35 years of age

10. Females of childbearing potential and males capable of fathering a child: Member has been counseled on the use of effective contraception during treatment (from start of mobilization through at least 6 months after administration of Casgevy) AND advised of the risks associated with conditioning agents

11. For females of childbearing potential: Member is not pregnant or breast-feeding: Negative serum pregnancy test within the past 30 days
    NOTE: A negative serum pregnancy test must be confirmed prior to the start of mobilization and re-confirmed prior to conditioning procedures and before Casgevy administration.

12. Negative testing for Human Immunodeficiency virus-1 negative, Human Immunodeficiency virus-2 negative, hepatitis B, hepatitis C, syphilis, Human T-Cell lymphotropic virus-1 and Human T-Cell lymphotropic virus-2, malaria, tuberculosis, toxoplasmosis, Trypanosoma cruzi or West Nile Virus

13. Member does not have a history of prior or current malignancy or myeloproliferative disorder or a significant immunodeficiency disorder

14. No history of significant bleeding disorder

CONTINUATION OF THERAPY

Repeat administration is experimental and investigational since the safety and efficacy beyond one treatment has not been studied and is not indicated in the current FDA approval for Casgevy. The evidence is insufficient to determine the effects on net health outcomes.

LIMITATIONS AND EXCLUSIONS

There are no contraindications listed in the manufacturer's labeling at this time, however concurrent administration of Category X drugs along with Casgevy is not indicated.

The following are considered **experimental, investigational, and unproven** based on insufficient evidence:

1. Any indications other than those listed above except for sickle cell anemia. See separate policy for criteria in sickle cell anemia.
2. Prior treatment with any form of HSCT, Casgevy, or other gene therapy

DURATION OF APPROVAL: Duration sufficient for **ONE** single course of treatment

PRESCRIBER REQUIREMENTS: Prescribed by, or in consultation with, a board-certified hematologist

AGE RESTRICTIONS: ≥ 12 years and ≤ 35 years at the time of infusion
The age across the trials was 12 to 35 years of age.

DOSING CONSIDERATIONS: Cell suspension for IV infusion. For autologous use only.

- Patients are required to undergo stem cell mobilization followed by apheresis to obtain $CD34^+$ cells for Casgevy manufacturing.
- Dosing is based on the number of $CD34^+$ cells in the infusion bag(s) per kg of body weight. Minimum recommended dose is 3×10^6 $CD34^+$ cells/kg
- Myeloablative conditioning must be administered before infusion of Casgevy.

ADMINISTRATION:

1. Casgevy is considered a provider-administered therapy in a Qualified Treatment Center by a physician(s) with experience in HSCT and in the treatment of patients with beta thalassemia.
2. Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or rendering a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Accelerated approval for Casgevy is based on results from interim analysis of one Phase 1/2/3 clinical trial, CLIMB-111.

Phase 1/2/3 Study Climb-111

The CLIMB SCD-111 trial (NCT03655678) is an international, multicenter, open-label, single arm study of 59 patients, ages 12-35 years of age with transfusion dependent beta thalassemia indicated by both genotype (bi-allelic pathogenic mutations in the beta globin gene and phenotype (transfusion dependence). Eligible participants required history of 100ml/Kg/yr or ≥ 10 units/yr of packed red blood cells in the last 2 years. Members were excluded if they had HLA-matched donor available, prior allo-HSCT, associated α-thalassemia and >1 alpha globin gene deletion or alpha multiplications, or sickle cell beta thalassemia variant. Participants were also excluded for clinically significant and active bacterial, viral, fungal, or parasitic infection as determined by the investigator, and white blood cell count <3 × 10^9/L or platelet count <50 × 10^9/L not related to hypersplenism.

Of the 59 enrolled patients 35 had been followed long enough post therapy to be included in the interim data analysis. The primary efficacy endpoint was the proportion of subjects achieving transfusion independence (TI) for 12 consecutive months with a total hemoglobin level ≥ 9 g/dl. 32 of 35 (91.4%) achieved the primary endpoint of TI for 12 months. All individuals meeting the primary endpoint maintained TI throughout the study period as of the last data cut. The median duration of TI was 20.8 months.

The main secondary endpoint was average total hemoglobin which rose to 13.1g/dl. Although three study participants

did not achieve TI for 12 months, their volume of annual transfusions went down by 79.8%, 83.9% and 97.9% as compared to baseline. Two of the three participants not reaching the primary endpoint did eventually reach transfusion independence and remained free of transfusions during follow-up (Locatelli et al 2024). The third participant had a relative reduction of 84% in annualized transfusions. This third patient did eventually become TI after more data was collected beyond the cutoff date for this publication.

Serum ferritin levels increased from baseline after exagamglogene but subsequently decreased below baseline. Of 35 participants 28, restarted iron chelation but 10 were able to stop chelation therapy

Serious adverse reactions after myeloablative conditioning and CASGEVY infusion were observed in 33% of patients with TDT. The most common serious adverse reactions (≥ 2 patients) were veno-occlusive liver disease, pneumonia, hypoxia, thrombocytopenia, viral infection, and upper respiratory tract infection. All serious adverse events resolved. There were no discontinuations or malignancies. Other side effects from Casgevy were similar to those that occur with autologous stem cell transplants. This included nausea, stomatitis, vomiting and febrile neutropenia. There were no significant safety events attributable to Casgevy. All patients were successful in neutrophil and platelet engraftment.

Final data for study CLIMB-111 has not been published yet.

The 15-year long term extension study, CLIMB -131 (NCT04208529), is an on-going, global, multi-site, rollover study designed to evaluate the safety and efficacy of Casgevy in subjects who previously received Casgevy in study 111 (for treatment of transfusion dependent thalassemia). Study 141 (NCT05356195) has started and is aimed at pediatric patients aged 2-11 years of age with TDT.

National and Specialty Organizations

The Institute for Clinical and Economic Research (ICER) has not evaluated cost effectiveness of Casgevy for transfusion-dependent thalassemia yet. A recent study (Udeze *et al*.2023) reviewed the health care resource utilization of individuals with TDT compared to matched controls without beta thalassemia and found that the lifetime costs of TDT is 7.1 million compared to 235,000 dollars for a person without TDT.

The national Institute for Healthcare Excellence recommended exagamglogene for people over 12 years of age when an HLA matched related donor was not available.

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

Code	Description
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96415	Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure)

HCPCS (Healthcare Common Procedure Coding System)

Code	Description
J3392	Injection, exagamglogene autotemcel, per treatment

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

02/12/2025	Edited introduction. Updated medical summary and references. No changes to criteria.
12/11/2024	Added requirement of Molina Medical Director review.
02/14/2024	New policy. IRO reviewed on January 31, 2024, by a practicing physician board certified in Pediatrics and Pediatric Hematology/Oncology.

REFERENCES

1. Benz EJ, Vichinsky EP, et al. Management of Thalassemia. Updated Jan 11, 2025. Accessed January 28, 2025. http://www.uptodate.com/.
2. Cappellini MD, Farmakis D, Porter J, et al., editors. 2021 Guidelines: For the Management of Transfusion Dependent Thalassaemia (TDT) [Internet]. 4th edition. Nicosia (Cyprus): Thalassaemia International Federation; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK603103/
3. CASGEVY (exagamglogene autotemcel), FDA Prescribing Information January 2024.: https://www.fda.gov/media/174615/download
4. ClinicalTrials.gov. CTX001-111: A Safety and Efficacy Study Evaluating CTX001 in Subjects with Transfusion-Dependent β-Thalassemia [ID: NCT03655678]. National Library of Medicine. Accessed January 29, 2025. http://clinicaltrials.gov.
5. ClinicalTrials.gov. CTX001-131: A Long-term Follow-up Study in Participants Who Received CTX001 [ID: NCT04208529]. National Library of Medicine. Accessed January 29, 2025. http://clinicaltrials.gov.
6. ClinicalTrials.gov. CTX001-141: Evaluation of Safety and Efficacy of CTX001 in Pediatric Participants With Transfusion-Dependent β-Thalassemia (TDT) [ID: NCT05356195]. National Library of Medicine. Accessed January 29, 2025. http://clinicaltrials.gov.
7. Corbacioglu S, Locatelli F, Lang P, et al. Abstract V907. Transfusion independence after exagamglogene autotemcel in patients with transfusion-dependent β-thalassemia. Oncol Res Treat. 2023;46:131-132. doi:10.1159/000533576
8. Eastern Cooperative Oncology Group (ECOG) Performance Status. https://ecog-acrin.org/resources/ecog-performance-status.
9. Farmakis D, Porter J, Taher A, et al. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia. Hemasphere. 2022 Jul 29;6(8):e732. doi: 10.1097/HS9.0000000000000732. PMID: 35928543; PMCID: PMC9345633.
10. Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia. N Engl J Med. 2021 Jan 21;384(3):252-260. doi: 10.1056/NEJMoa2031054. Epub 2020 Dec 5. PMID: 33283989.
11. Hayes. Health technology assessment: Exagamglogene Autotemcel (Vertex/CRISPR) for Transfusion dependent Beta thalassemia. Published October 22, 2024. https://evidence.hayesinc.com/report/pg.exacelTDT. Accessed January 22, 2025.
12. Locatelli F, Lang, P, Corbacioglu, S, et al. 2023. Abstract S270. Transfusion independence after exagamglogene autotemcel in patients with transfusion-dependent beta-thalassemia. https://library.ehaweb.org/eha/2023/eha2023-congress/387970/
13. Locatelli F, Lang P, Wall D, Meisel R, Corbacioglu S, Li AM, de la Fuente J, Shah AJ, Carpenter B, Kwiatkowski JL, Mapara M, Liem RI, Cappellini MD, Algeri M, Kattamis A, Sheth S, Grupp S, Handgretinger R, Kohli P, Shi D, Ross L, Bobruff Y, Simard C, Zhang L, Morrow PK, Hobbs WE, Frangoul H; CLIMB THAL-111 Study Group. Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia. N Engl J Med. 2024 May 9;390(18):1663-1676. doi: 10.1056/NEJMoa2309673. Epub 2024 Apr 24. PMID: 38657265.
14. National Institute for Health care Excellence: Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia in people 12 years and over. Technology appraisal guidance, September 11, 2024
15. National Organization for Rare Disorders (NORD). Beta thalassemia. Accessed December 2023. https://www.rarediseases.org.
16. Udeze C., Evans KA., et al., Economic and clinical burden of managing Transfusion-Dependent b-Thalassemia in the United States. Journal of Medical Economics, 26(1), pp.924-932. 2023.
17. Viprakasit V, Origa R. Genetic basis, pathophysiology and diagnosis. In: 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. Chapter 1. Accessed December 20, 2023