exagamglogene autotemcel (Casgevy™)

Medicare Advantage Medical Policy # 082
Original Effective Date: 04/01/2025
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Applies to all products administered or underwritten by, the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider the use of exagamglogene autotemcel (Casgevy™)‡ for the treatment of sickle cell disease or transfusion-dependent β-thalassemia to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for exagamglogene autotemcel (Casgevy) will be considered when the following criteria are met:

- Patient is greater than or equal to 12 years of age; AND
- Provider attests to consideration of the use of prophylaxis therapy for seizures prior to initiating myeloablative conditioning; AND
- Patient has been screened and found negative for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus 1 & 2 (HIV-1/HIV-2) in accordance with clinical guidelines prior to leukapheresis; AND
- Casgevy will not be administered concurrently with live vaccines while the patient is immunosuppressed; AND
- Patient does not have a history of hypersensitivity to dimethyl sulfoxide (DMSO) or dextran 40; AND
- Patient has not received other gene therapies [e.g., lovotibeglogene autotemcel (Lyfgenia®)‡, betibeglogene autotemcel (Zynteglo®)‡, etc]; AND
- Patient will not receive therapy concomitantly with any of the following:
    - Iron chelators for 7 days prior to mobilization and 6 months post-treatment (3-months post-treatment for non-myelosuppressive iron chelators); AND
    - Disease modifying agents (e.g., hydroxyurea or crizanlizumab) for at least 8 weeks prior to mobilization and conditioning; AND
- Patient is a candidate for autologous hematopoietic stem cell transplant (HSCT) and has not had prior autologous or allogeneic HSCT; AND
- For patients under 18 years of age, the patient does not have a known and suitable 10/10 human leukocyte antigen (HLA) matched related donor willing to participate in an allogeneic HSCT; AND

- For patients being treated for sickle cell disease, patient meets ALL of the following:
    - Patient has a confirmed diagnosis of sickle-cell disease with one of the following genotypes βS/βS or βS/β0 or βS/β+ (Note: Additional genotypes will be considered on a case-by-case basis based on disease severity) as determined by one of the following:
        - Identification of significant quantities of HbS with or without an additional abnormal β-globin chain variant by hemoglobin assay; OR
        - Identification of biallelic *HBB* pathogenic variants where at least one allele is the p.Glu6Val pathogenic variant on molecular genetic testing; AND
    - Patient has symptomatic disease despite treatment with hydroxyurea at any point in the past OR add-on therapy (e.g., crizanlizumab, voxelotor, etc.) OR has experienced intolerance to these therapies; AND
    - Patient experienced two or more vaso-occlusive event/crises (defined as acute episodes of pain requiring a medical facility visit and treatment with oral or parenteral narcotic agents or a parenteral non-steroidal anti-inflammatory drug [NSAID]) in the previous year; AND
    - Patient will be transfused prior to apheresis to a total Hb $\leq$ 11 g/dL and a HbS level < 30% and patient will be transfused at least 8 weeks prior to initiation of myeloablative conditioning (with aforementioned Hb and HbS goals); AND
    - Patient will not receive granulocyte-colony stimulating factor (G-CSF) for the mobilization of hematopoietic stem cells (HSC); OR
- For patients being treated for Beta Thalassemia, patient meets ALL of the following:
    - Patient has a documented diagnosis of homozygous beta thalassemia or compound heterozygous beta thalassemia including β-thalassemia/hemoglobin E (HbE) as outlined by the following:
        - Diagnosis is confirmed by *HBB* sequence gene analysis showing biallelic pathogenic variants; OR
        - Patient has severe microcytic hypochromic anemia, absence of iron deficiency, anisopoikilocytosis with nucleated red blood cells on peripheral blood smear, and hemoglobin analysis that reveals decreased amounts or complete absence of hemoglobin A (HbA) and increased HbA_2 with or without increased amounts of hemoglobin F (HbF); AND
    - Patient has transfusion-dependent disease defined as a history of transfusions of at least 100 mL/kg/year or $\geq$ 10 units/year of packed red blood cells (pRBCs) in the 2 years preceding therapy; AND
    - Patient will be transfused prior to apheresis to a total Hb $\geq$ 11 g/dL for 60 days prior to myeloablative conditioning; AND
    - Patient does NOT have ANY of the following:
        - Severely elevated iron in the heart (i.e., patients with cardiac T2* less than 10 msec by magnetic resonance imaging [MRI] or left ventricular ejection fraction [LVEF] < 45% by echocardiogram); OR

- Advanced liver disease [i.e., AST or ALT > 3 times the upper limit of normal, or direct bilirubin value > 2.5 times the upper limit of normal, or if a liver biopsy demonstrated bridging fibrosis or cirrhosis]

When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of exagamglogene autotemcel (Casgevy) when the patient has received other gene therapies, when the patient does not have symptomatic disease despite treatment with or intolerance to a disease modifying agent, or when the patient is under 18 years of age and has a known and suitable HLA matched donor willing to participate in an allogeneic HSCT to be **not medically necessary.****

Based on review of available data, the Health Plan considers the use of exagamglogene autotemcel (Casgevy) for the treatment of beta thalassemia when the patient has severely elevated iron in the heart or advanced liver disease to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of exagamglogene autotemcel (Casgevy) when the patient selection criteria are not met (except those denoted above to be **not medically necessary****) to be **investigational.***

Background/Overview

Casgevy is an autologous hematopoietic stem cell (HSC)-based gene therapy indicated for the treatment of patients ≥ 12 years of age with sickle cell disease with recurrent vaso-occlusive crises or transfusion-dependent β-thalassemia. Treatment with Casgevy involves removal of a patient's CD34+ hematopoietic stem cells which are modified using the CRISPR/Cas9 process to increase the production of fetal hemoglobin (HbF) in red blood cells and improve their oxygen-carrying capacity. Casgevy is administered via intravenous (IV) infusion following myeloablative conditioning. The administration and preparation process are complex and require hospitalization of the recipient. The time between autologous cell collection and shipment of genetically modified cells back to the authorized treatment center is estimated to be about 5 to 6 months. Prior to cell collection, patients must receive 8 weeks of RBC transfusions, which extends the total treatment time to a minimum of 7 to 8 months. After Casgevy administration, patients should follow standard procedures for patient management after HSC transplantation including irradiating any blood products required within the first 3 months after infusion and avoiding the use of non-myelosuppressive iron chelators for at least 3 months and the use of myelosuppressive iron chelators for at least 6 months of infusion. Patients treated with Casgevy should not donate blood, organs, tissues, or cells at any time in the future.

Sickle Cell Disease
Sickle cell disease is a group of inherited red blood cell disorders in which the hemoglobin is abnormal and leads to "sickling" of the red blood cells. This reduces the ability of the blood to transport oxygen to the body and can result in blocked blood vessels and tissue ischemia which manifest as various complications. Complications of sickle cell disease include acute vaso-occlusive crises/events (VOCs/VOEs) such as acute pain crises, splenic sequestration, acute chest syndrome, stroke, retinal damage, priapism, joint problems, and others. Patients with sickle cell disease have a shorter life expectancy than race-matched peers and often have a low quality of life due to frequent crises. Current pharmacologic treatment options for sickle cell disease include hydroxyurea (Droxia®, Siklos®, Hydrea®)‡, L-glutamine (Endari™)‡, and crizanlizumab (Adakveo®)‡. Additionally, Casgevy and another gene therapy, Lyfgenia, are now approved for treatment of patients with sickle cell disease and recurrent VOCs. The most recent National Institutes of Health-National Heart, Lung, and Blood Institute Evidence-based management of sickle cell disease guidelines were published in 2014 and do not include Endari, Adakveo, Casgevy, or Lyfgenia. These guidelines note that only hydroxyurea and chronic blood transfusions are proven to be disease-modifying treatments for this condition. They recommend hydroxyurea therapy in most adult sickle cell disease patients as well as all pediatric patients $\geq$ 9 months of age.

β-thalassemia
β-thalassemia is an inherited blood disorder caused by a mutation of the hemoglobin beta (*HBB*) gene responsible for making the beta-globin protein. When this protein is absent, the disease is referred to as beta-zero (β0) thalassemia. Whereas if the protein is simply reduced in function, the disease is referred to as beta-plus (β+) thalassemia. The condition can be further classified by severity. β-thalassemia major is associated with severe symptoms of anemia diagnosed in childhood while patients with β-thalassemia minor may be asymptomatic or exhibit minor anemia. Thalassemia indermedia has a variable severity with a broad range of symptoms between the minor and major forms. Recently, patients have been classified according to their transfusion status (i.e., transfusion-dependent β-thalassemia or non-transfusion-dependent β-thalassemia). Clinical studies typically define "transfusion dependence" as a history of at least 100 mL/kg/year of peripheral red blood cells or $\geq$ 8 transfusions of peripheral red blood cells per year for the prior 2 years. Symptoms of β-thalassemia include shortness of breath, fatigue, weakness, dizziness, jaundice, and/or headaches. Failure to thrive is observed in affected infants. If untreated, bone deformities may develop and overall disease complications lead to a short life span. Even with treatment, severe complications may arise due to iron overload secondary to increased intestinal absorption and frequent blood transfusions.

The main treatment option available for transfusion dependent β-thalassemia is blood transfusion to improve anemia and suppress ineffective erythropoiesis. Transfusions also prevent the majority of skeletal and neurological complications of the disease, but are associated with severe complications such as alloimmunization, transmissions of infectious disease, and iron overload. Typically, blood transfusions are initiated based on inability of the patient to compensate for low hemoglobin, increases in symptoms for ineffective erythropoiesis, or initial hemoglobin levels < 6 g/dL. Transfusions are usually given once every 3-4 weeks and the amount of blood transfused varies

based on the pretransfusion hemoglobin levels (typical target is 9-10 g/dL). Additional treatments for this condition include chelation therapy for patients with iron overload, splenectomy when hypersplenism increases transfusion requirements, hydroxyurea, luspatercept-aamt (Reblozyl®)‡ to decrease transfusion burden, and allogeneic hematopoietic cell transplant (HCT) for patients with an HLA-matched sibling donor for whom the benefit outweighs the risks. Although allogeneic HCT is considered curative, only approximately 25% of patients have a matched sibling donor and the likelihood of success decreases with patient age. There are now two gene therapies, Zynteglo and Casgevy, approved to provide a curative treatment option for patients who may not be candidates for HCT based on lack of a suitable donor.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Casgevy is approved for the treatment of patients aged 12 years and older with:

- Sickle cell disease with recurrent vaso-occlusive crises
- Transfusion-dependent β-thalassemia

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Sickle Cell Disease

The safety and efficacy of Casgevy in adult and adolescent patients with sickle cell disease have been evaluated in a single-arm, multi-center trial. Eligible patients underwent mobilization and apheresis to collect CD34+ stem cells for Casgevy manufacture, followed by myeloablative conditioning and infusion of Casgevy. Patients were then followed for 24 months after Casgevy infusion and encouraged to enroll in an ongoing long-term follow-up trial for additional follow-up for a total of 15 years after Casgevy infusion.

Patients were eligible for the trial if they had a history of at least 2 protocol-defined severe vaso-occlusive crisis (VOC) events during each of the 2 years prior to screening. In this trial, severe VOC is defined as an occurrence of at least one of the following events:

- Acute pain event requiring a visit to a medical facility and administration of pain medications or RBC transfusions
- Acute chest syndrome
- Priapism lasting > 2 hours and requiring a visit to a medical facility
- Splenic sequestration

Patients were excluded if they had advanced liver disease, history of untreated Moyamoya disease, or presence of Moyamoya disease that in the opinion of the investigator put the patient at risk of bleeding. Patients aged 12-16 years were required to have normal transcranial doppler (TCD), and patients aged 12 to 18 years were excluded if they had any history of abnormal TCD in the middle cerebral artery and the internal carotid artery. Patients with an available 10/10 human leukocyte antigen matched related hematopoietic stem cell donor were excluded. Patients with more than 10 unplanned hospitalizations or emergency department visits related to chronic pain rather than SCD-related acute pain crises in the year before screening were excluded.

At the time of the interim analysis, a total of 63 patients were enrolled in the trial, of which 58 (92%) patients had started mobilization. A total of 44 (76%) of patients had received Casgevy infusion and formed the full analysis set (FAS). Thirty-one patients from the FAS (70%) had adequate follow-up to allow evaluation of the primary efficacy endpoint and formed the primary efficacy set (PES). The interim analysis was conducted with the PES at a median (min, max) total duration of follow-up of 26.0 (17.8, 48.1) months from the time of Casgevy infusion. There were no cases of graft failure or graft rejection.

The primary efficacy outcome was the proportion of VF12 responders, defined as patients who did not experience any protocol-defined severe VOCs for at least 12 consecutive months within the first 24 months after Casgevy infusion. The proportion of patients who did not require hospitalization due to severe VOCs for at least 12 consecutive months within the 24-month evaluation period (HF12) was also assessed. The evaluation of VF12 and HF12 began 60 days after the last RBC transfusion for post-transplant support or SCD management. The median (min, max) time to the last RBC transfusion was 19 (11, 52) days following Casgevy infusion for patients in the primary efficacy set. The VF12 response rate was 29/31 (93.5%; 98% one-sided CI: 77.9%, 100.0%). One VF12 responder, after initially achieving a VF12 response, experienced an acute pain episode meeting the definition of a severe VOC at Month 22.8 requiring a 5-day hospitalization; this patient was reported to have a parvovirus B19 infection at the time. Of the 31 patients evaluable for VF12 response, one patient was not evaluable for HF12 response; the remaining 30 patients (100%, 98% one-sided CI: 87.8%, 100.0%) achieved the endpoint of HF12.

Transfusion-dependent β-thalassemia
The safety and efficacy of Casgevy in adult and adolescent patients with transfusion-dependent β-thalassemia have been evaluated in an open-label, multi-center, single-arm trial. Eligible patients underwent mobilization and apheresis to collect CD34+ stem cells for Casgevy manufacture, followed by myeloablative conditioning and infusion of Casgevy. Patients were then followed for 24 months after Casgevy infusion and encouraged to enroll in an ongoing long-term follow-up trial for additional follow-up for a total of 15 years after Casgevy infusion.

Patients were eligible for the trial if they had a history of requiring at least 100 mL/kg/year or 10 units/year of RBC transfusions in the 2 years prior to enrollment. Patients were excluded if they had severely elevated iron in the heart (i.e., patients with cardiac T2* less than 10 msec by MRI or left ventricular ejection fraction < 45% by echocardiogram) or advanced liver disease. Patients were also

excluded if they had an available 10/10 human leukocyte antigen matched related hematopoietic stem cell donor.

At the time of the interim analysis, a total of 59 patients enrolled in the trial, of which 59 (100%) started mobilization. A total of 52 (88%) patients received Casgevy infusion and formed the full analysis set (FAS). Thirty-five patients from the FAS (67%) had adequate follow-up to allow evaluation of the primary efficacy endpoint and formed the primary efficacy set (PES). The interim analysis was conducted with the PES at a median (min, max) duration of follow up of 23.8 (16.1, 48.1) months from the time of Casgevy infusion. There were no cases of graft failure or graft rejection.

The primary outcome was the proportion of patients achieving transfusion independence for 12 consecutive months (TI12), defined as maintaining weighted average Hb $\geq$ 9 g/dL without RBC transfusions for at least 12 consecutive months any time within the first 24 months after Casgevy infusion in the trial, evaluated starting 60 days after the last RBC transfusion for post-transplant support or TDT disease management. The TI12 responder rate was 32/35 (91.4%, 98.3% one-sided CI: 75.7%, 100%). All patients who achieved TI12 remained transfusion-independent with a median (min, max) duration of transfusion-independence of 20.8 (13.3., 45.1) months and normal mean weighted average total Hb levels (mean [SD] 13.1 [1.4] g/dL). The median (min, max) time to last RBC transfusion for patients who achieved TI12 was 30 (11, 91) days following Casgevy infusion. Three patients did not achieve TI12. These patients had reductions in annualized transfusion frequency of 78.6%, 67.4%, and 94.6% respectively, compared to baseline requirements.

References

1. Casgevy [package insert]. Vertex Pharmaceuticals, Inc. Boston, MA. Updated January 2024
2. Casgevy Drug Evaluation. Express Scripts. Updated December 2023.
3. Casgevy New Drug Review. IPD Analytics. Updated December 2023.
4. The National Institutes of Health—National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease, Expert Panel Report 2014. Available at: https://www.nhlbi.nih.gov/resources/evidence-based-management-sickle-cell-disease-expert-panel-report-2014

Policy History

Original Effective Date: 04/01/2025
Current Effective Date: 04/01/2025
01/21/2025 UM Committee Review. New policy.
Next Scheduled Review Date: 01/2026

Coding

The five character codes included in the Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of the Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J3392
ICD-10 Diagnosis	D56.1, D57.00-D57.819

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);

2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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 that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide

to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.