MEDICAL COVERAGE POLICY	
SERVICE:	**Casgevy™ (Exagamglogene autotemcel)**
Policy Number:	**310**
Effective Date:	**9/1/2024**
Last Review:	**6/10/2024**
Next Review:	**6/10/2025**

Important note: *Unless otherwise indicated, medical policies will apply to all lines of business. Medical necessity as defined by this policy does not ensure the benefit is covered. This medical policy does not replace existing federal or state rules and regulations for the applicable service or supply. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan documents. See the member plan specific benefit plan document for a complete description of plan benefits, exclusions, limitations, and conditions of coverage. In the event of a discrepancy, the plan document always supersedes the information in this policy.*

SERVICE: Exagamglogene autotemcel (Casgevy™)

PRIOR AUTHORIZATION: Required

POLICY: Please review the plan's EOC (Evidence of Coverage) or Summary Plan Description (SPD) for details.

For Medicare plans, please refer to appropriate Medicare NCD (National Coverage Determination) or LCD (Local Coverage Determination). Medicare NCD or LCD specific InterQual criteria may be used when available. If there are no applicable NCD or LCD criteria, use the criteria set forth below.

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid Provider Procedures Manual | TMHP (TMPPM). Texas Mandate HB154 is applicable for Medicaid plans. If there are no applicable criteria to guide medical necessity decision making in the TMPPM, refer to InterQual. If there are no applicable criteria to guide medical necessity decision making in the TMPPM or InterQual, use the criteria set forth below.

Baylor Scott & White Health Plan (BSWHP) may consider exagamglogene autotemcel (Casgevy™) medically necessary for the treatment of Sickle Cell Disease (SCD) when ALL of the following criteria are met:

1. Exagamglogene is being prescribed by or in consultation with a board-certified hematologist; **AND**
2. Member is 12 years of age or older, but less than or equal to 50 years of age; **AND**
3. Member has a Karnofsky performance status of ≥60% for subjects ≥ 16 years of age or Lansky performance status of ≥60% for subjects <16 years of age; **AND**
4. Member has one of the following genotypes confirmed by molecular or genetic testing:
   a) βS/βS
   b) $\beta S/\beta^0$
   c) $\beta S/\beta^+$; **AND**
5. Member will receive exagamglogene autotemcel at an activated authorized treatment center; **AND**
6. Member has experienced hydroxyurea failure, intolerance, or has a contraindication; **AND**
7. Member is eligible for an autologous hematopoietic stem cell transplant (aHSCT); **AND**
8. Member does Not have an available human leukocyte antigen (HLA)-matched related donor; **AND**

9. Member has Not received any of the following:
   a) Hematopoietic stem cell transplant (HSCT)
   b) Exagamglogene autotemcel or any other gene therapy for SCD
   c) Investigational cellular therapy for SCD; **AND**
10. Exagamglogene autotemcel will Not be used concomitantly with other gene editing therapies for SCD; **AND**
11. Exagamglogene autotemcel will be dosed and administered according to FDA approved labeling; **AND**
12. Member has documented history of at least 2 severe vaso-occlusive episodes (sVOE) per year while receiving appropriate supportive care (e.g., pain management plan, hydroxyurea) during the previous two years

    Severe vaso-occlusive episode (sVOE) defined as:

    a) Acute pain events that required a visit to a medical facility and administration of pain medications (opioids or intravenous non-steroidal anti-inflammatory drugs) or RBC transfusions
    b) Acute chest syndrome, as indicated by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever
    c) Priapism lasting >2 hours and requiring a visit to a medical facility
    d) Splenic sequestration, as defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in hemoglobin concentration of ≥2 g/dL
    e) Acute hepatic sequestration, defined by a sudden increase in liver size associated with pain in the right upper quadrant, abnormal results of liver function test not due to biliary tract disease, and reduction in Hb concentration by ≥2 g/dL below the baseline value; AND
13. Member does Not have any of the following:
    a) White Blood Cell (WBC) count <3 × 10^9/L
    b) Platelet count <50 × 10^9/L, not related to hypersplenism
    c) Fetal hemoglobin (HbF) level >15%
    d) Left ventricular ejection fraction (LVEF) <45% by echocardiogram
    e) Baseline estimated glomerular filtration rate <60 mL/min/1.73 m2
    f) Advanced liver disease, as defined by any one of the following:
       I. Alanine transaminase (ALT) >3 × the upper limit of normal (ULN)
       II. Direct bilirubin value >2.5 × ULN
       III. Baseline prothrombin time (INR >1.5 × ULN)
       IV. History of cirrhosis
       V. Any evidence of bridging fibrosis
       VI. Active hepatitis on liver biopsy
    g) Clinically significant and active bacterial, viral, fungal, or parasitic infection
    h) Any prior or current malignancy or myeloproliferative disorder
    i) A significant immunodeficiency disorder
    j) History of untreated Moyamoya disease or Moyamoya disease that puts the member at risk of bleeding

k) Positive for the presence of any of the following:
   I. Human immunodeficiency virus-1 (HIV-1) or Human immunodeficiency virus-2 (HIV-2) (positive antigen/antibody AND nucleic acid tests [NAT])
   II. Hepatitis B virus (HBV) (positive Hepatitis B core antibody [HBcAb] AND NAT tests)
   III. Hepatitis C virus (HCV; positive antibody [HCAb] AND NAT tests)
l) Intolerance, contraindication, or known sensitivity to plerixafor or busulfan
m) Prior anaphylactic reaction with excipients (dimethylsulfoxide [DMSO], dextran)
n) Pregnancy or breastfeeding
o) History of a significant bleeding disorder

Only ONE dose per lifetime is medically necessary.

All requests will be reviewed by a clinical pharmacist and medical director.

BSWHP considers exagamglogene autotemcel (Casgevy™) for the treatment of all other indications to be experimental, investigational, and/or unproven.

BACKGROUND:

Sickle Cell Disease (SCD) is a single-gene disorder in which 1 DNA base-pair alteration in the gene coding for hemoglobin produces sickle hemoglobin (HbS) when inherited in an autosomal recessive fashion with a second HbS or when combined with other hemoglobin variants (e.g., HbC or β-thalassemia). When deoxygenated within capillary beds sickle hemoglobin forms long chains which distorts the red blood cell (RBC) into a sickle shape. Sickled RBCs have increased adhesion molecules compared to normal RBCs that facilitate binding to endothelial walls. In addition, Sickle cells hemolyze rapidly. Recurrent RBC sickling and hemolysis, combined with endovascular inflammation, result in acute and chronic organ damage at the cellular level, associated with acute, unpredictable, and potentially life-threatening complications.[1]

In the US, approximately 100,000 people have SCD. Children born in the US may be diagnosed shortly after birth through newborn screening programs. SCD is characterized by hemolytic anemia, acute and chronic pain, acute chest syndrome; increased incidence of stroke, nephropathy, and retinopathy; and a life span that is 20 years shorter than the general population.[1] A cure for SCD today is a stem cell transplant from a matched donor, but this option is only available to a small fraction of patients living with SCD because of the lack of available donors.[3]

Exagamglogene autotemcel (Casgevy™) is an autologous genome edited hematopoietic stem cell-based gene therapy indicated for the treatment of SCD in patients 12 years and older with recurrent vaso-occlusive crises (VOCs).[2]

Casgevy is a cellular gene therapy consisting of autologous CD34+ Hematopoietic Stem Cells (HSC) edited by CRISPR/CAs9-technology at the erythroid specific enhancer region of the BCL11A gene to

reduce BCL11A expression in erythroid lineage cells, leading to increased fetal hemoglobin (HbF) protein production.[2]

Casgevy is prepared from the patient's own HSCs, which are obtained via apheresis procedure(s). The autologous cells are enriched for CD34+ cells, and then genome edited ex vivo by introducing the CRISPR/Cas9 ribonucleoprotein (RNP) complex by electroporation. The guide RNA included in the RNP complex enables CRISPR/Cas9 to make a precise DNA double-strand break at a critical transcription factor binding site (GATA1) in the erythroid specific enhancer region of the BCL11A gene. As a result of the editing, GATA1 binding is disrupted and BCL11A expression is reduced. This reduction in BCL11A expression conversely results in an increase in gamma-globin expression and downstream fetal hemoglobin formation.[2]

The edited CD34+ cells are formulated into a suspension in a sterile cryo-preservative medium and cryopreserved. Casgevy is shipped as a frozen suspension in patient-specific vial(s). The product is thawed prior to infusion, and administered as a HSC transplant.[2]

After Casgevy infusion, the edited CD34+ cells engraft in the bone marrow and differentiate to erythroid lineage cells with reduced BCL11A expression. Reduced BCL11A expression results in an increase in γ-globin expression and HbF protein production in erythroid cells. In patients with severe sickle cell disease, HbF expression reduces intracellular hemoglobin S (HbS) concentration, preventing the red blood cells from sickling and addressing the underlying cause of disease, thereby eliminating VOCs.[2]

Trial 1 (NCT03745287, CLIMB-121) is an ongoing single-arm, multi-center trial evaluating the safety and efficacy of a single dose of Casgevy in adult and adolescent patients with sickle cell disease. 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 in Trial 1 for 24 months after Casgevy infusion.[2]

At the time of the interim analysis, a total of 63 patients enrolled in the trial, of which 58 (92%) patients started mobilization. A total of 44 (76%) patients 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).[2]

An interim analysis (IA) was conducted with 31 patients eligible for the primary efficacy analysis, i.e., the primary efficacy set (PES). The median (min, max) total duration of follow up was 19.3 (0.8, 48.1) months from the time of Casgevy infusion in FAS. There were no cases of graft failure or graft rejection.[2]

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 in Trial 1. 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.[2]

The interim analysis occurred at the time when the alpha spending was approximately 0.02 for a one-sided test, when 31 patients were evaluable for VF12 responder status. The VF12 response rate was 29/31 (93.5%, 98% one-sided CI: 77.9%, 100.0%). The 29 VF12 responders did not experience protocol defined severe VOCs during the evaluation period with a median duration of 22.2 months at the time of the interim analysis. 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.[2]

CODES:

Important note: *Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.*

CPT Codes:	96413 - Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug	
HCPCS Codes:	J3590 - Unclassified biologics	
ICD10 codes:	D57.00	Hb-Ss Disease With Crisis, Unspecified
	D57.01	Hb-Ss Disease With Acute Chest Syndrome
	D57.02	Hb-Ss Disease With Splenic Sequestration
	D57.03	Hb-Ss Disease With Cerebral Vascular Involvement
	D57.04	Hb-Ss Disease With Dactylitis
	D57.09	Hb-Ss Disease With Crisis With Other Specified Complication
	D57.1	Sickle-Cell Disease Without Crisis
	D57.20	Sickle-Cell/Hb-C Disease Without Crisis
	D57.211	Sickle-Cell/Hb-C Disease With Acute Chest Syndrome
	D57.212	Sickle-Cell/Hb-C Disease With Splenic Sequestration
	D57.213	Sickle-Cell/Hb-C Disease With Cerebral Vascular Involvement
	D57.214	Sickle-Cell/Hb-C Disease With Dactylitis
	D57.218	Sickle-Cell/Hb-C Disease With Crisis With Other Specified Complication
	D57.219	Sickle-Cell/Hb-C Disease With Crisis, Unspecified
	D57.40	Sickle-Cell Thalassemia Without Crisis
	D57.411	Sickle-Cell Thalassemia, Unspecified, With Acute Chest Syndrome
	D57.412	Sickle-Cell Thalassemia, Unspecified, With Splenic Sequestration
	D57.413	Sickle-Cell Thalassemia, Unspecified, With Cerebral Vascular Involvement
	D57.414	Sickle-Cell Thalassemia, Unspecified, With Dactylitis
	D57.418	Sickle-Cell Thalassemia, Unspecified, With Crisis With Other Specified Complication
	D57.419	Sickle-Cell Thalassemia, Unspecified, With Crisis
	D57.42	Sickle-Cell Thalassemia Beta Zero Without Crisis
	D57.431	Sickle-Cell Thalassemia Beta Zero With Acute Chest Syndrome
	D57.432	Sickle-Cell Thalassemia Beta Zero With Splenic Sequestration
	D57.433	Sickle-Cell Thalassemia Beta Zero With Cerebral Vascular Involvement
	D57.434	Sickle-Cell Thalassemia Beta Zero With Dactylitis
	D57.438	Sickle-Cell Thalassemia Beta Zero With Crisis With Other Specified Complication
	D57.439	Sickle-Cell Thalassemia Beta Zero With Crisis, Unspecified

	D57.44	Sickle-Cell Thalassemia Beta Plus Without Crisis
	D57.451	Sickle-Cell Thalassemia Beta Plus With Acute Chest Syndrome
	D57.452	Sickle-Cell Thalassemia Beta Plus With Splenic Sequestration
	D57.453	Sickle-Cell Thalassemia Beta Plus With Cerebral Vascular Involvement
	D57.454	Sickle-Cell Thalassemia Beta Plus With Dactylitis
	D57.458	Sickle-Cell Thalassemia Beta Plus With Crisis With Other Specified Complication
	D57.459	Sickle-Cell Thalassemia Beta Plus With Crisis, Unspecified
	D57.80	Other Sickle-Cell Disorders Without Crisis
	D57.811	Other Sickle-Cell Disorders With Acute Chest Syndrome
	D57.812	Other Sickle-Cell Disorders With Splenic Sequestration
	D57.813	Other Sickle-Cell Disorders With Cerebral Vascular Involvement
	D57.814	Other Sickle-Cell Disorders With Dactylitis
	D57.818	Other Sickle-Cell Disorders With Crisis With Other Specified Complication
	D57.819	Other Sickle-Cell Disorders With Crisis, Unspecified
ICD10 Not covered:		

POLICY HISTORY:

Status	Date	Action
New	6/10/2024	New Policy

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and make modifications based upon the evolution of the published clinical evidence. Should additional scientific studies become available, and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

1. Kavanagh PL, Fasipe T, Wun T. Sickle cell disease. *JAMA*. 2022;328(1):57. doi:10.1001/jama.2022.10233
2. FDA Label Casgevy™ (Exagamglogene autotemcel). Food and Drug Administration
3. Vertex and CRISPR Therapeutics Announce US FDA Approval of CASGEVY™ (exagamglogene autotemcel) for the Treatment of Sickle Cell Disease | Vertex Pharmaceuticals Newsroom. Vertex Pharmaceuticals Newsroom. https://news.vrtx.com/news-releases/news-release-details/vertex-and-crispr-therapeutics-announce-us-fda-approval
4. Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-CAS9 gene editing for sickle cell disease and B-Thalassemia. *The New England Journal of Medicine*. 2021;384(3):252-260. doi:10.1056/nejmoa2031054

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White Insurance Company are wholly owned subsidiaries of Scott and White Health Plan. These companies are referred to collectively in this document as Baylor Scott & White Health Plan.

RightCare STAR Medicaid plans are offered through Scott and White Health Plan in the Central Managed Care Service Area (MRSA) and STAR and CHIP plans are offered through SHA LLC dba FirstCare Health Plans (FirstCare) in the Lubbock and West MRSAs.