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Crizanlizumab-tmca

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Crizanlizumab-tmca (Adakveo®) **may be considered medically necessary** when **ALL** of the following criteria are met, and the individual:

- Is 16 years of age or older, AND
- Has a diagnosis of sickle cell disease, AND
- Has experienced at least 2 sickle cell crises (i.e., medical facility visit for sickle cell-related pain, chest syndrome, priapism, or splenic sequestration) in the previous 12 months.

Crizanlizumab-tmca (Adakveo®**) is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications.

Policy Guidelines

None.

Description

Crizanlizumab-tmca (Adakveo®)
Adakveo® contains a monoclonal antibody, a molecule made in the laboratory to bind P-selectin, a protein that is found on the surface of endothelial cells (the cells that line the inner walls of blood vessels) and in platelets (blood cells that are involved in clotting).

P-selectin normally works to control the flow of white blood cells through blood vessels and how they adhere to blood vessel walls during periods of inflammation and tissue repair, such as after an injury. In sickle cell disease, P-selectin contributes to the adhesion of sickle red blood cells (cells with an abnormal crescent shape) to blood vessels, preventing blood flow through smaller vessels. This causes inflammation and vaso-occlusive pain crises.

By blocking or inhibiting P-selectin, Adakveo prevents this adhesion molecule from starting the process that leads to blood vessel occlusion, inflammation, and pain, and helps to maintain normal blood flow.

Sickle Cell Disease
Sickle cell disease (SCD) is an inherited group of disorders that affects hemoglobin, the molecule in the red blood cells that delivers oxygen to cells throughout the body. People with SCD are born with two sickle cell genes, one from each parent. In SCD, hemoglobin transforms

into stiff rods. Consequently, red blood cells which should be disc-shaped, become crescent, or sickle shaped. (2)

People with SCD start to have signs of the disease during the first year of life, usually around 5 or 6 months of age. Early symptoms may include fatigue or fussiness from anemia, painful swelling of the hands and feet, or a yellowish color of the skin (jaundice) or the whites of the eyes (icterus).

The signs and symptoms of SCD are caused by the sickling of red blood cells. The sickle cells usually only last 10 to 20 days, instead of the normal 90 to 120 days. When red blood cells sickle, they become inflexible and cannot easily change shape. Many break down prematurely as they move throughout the blood vessels, which can lead to anemia. The sickle-shaped cells can also stick to vessel walls, causing a blockage that slows or stops the flow of blood. When this happens, oxygen can't reach nearby tissues. The lack of oxygen can cause attacks of sudden, severe pain, called pain crises. Attacks can occur without warning. The effects of SCD vary from person to person and can change over time. Most of the signs and symptoms of SCD are related to complications of the disease. (2)

In the United States, about 1 in 13 Black or African American babies are born with sickle cell trait and about 1 in 365 Black or African American babies are born with sickle cell disease. Sickle cell disease also affects some people who come from Hispanic, southern European, Middle Eastern, or Asian Indian backgrounds.

Treatments for SCD may focus on relieving symptoms and lessening complications. They may include medications to prevent red blood cells from sickling, pain relievers, antibiotics to attempt to prevent infections in younger children, and blood transfusions to treat anemia. Other treatments such as bone marrow transplantation or gene therapies may be considered, depending on the severity of the SCD. (2)

<u>Sickle Cell Crisis</u>

SCD results in anemia and “sickle cell crisis” (SCC). The main clinical feature of SCD is the ''acute painful crisis,'' which often requires hospitalization. The term "sickle cell crisis" is used to describe several acute conditions such as the vaso-occlusive crisis (acute painful crisis), aplastic crisis, splenic sequestration crisis, hyperhemolytic crisis, hepatic crisis, dactylitis, and acute chest syndrome. Other acute complications include pneumonia, meningitis, sepsis and osteomyelitis, stroke, avascular necrosis, priapism, and venous thromboembolism. (3)

Vaso-occlusive Crisis (VOC)

Patients present with moderate to severe pain, which has variable intensity and frequency. Young children can have severe pain and swelling of both hands and feet (dactylitis). Most patients with SCD experience pain by the age of 6 years. Pain can begin from any part of the body but frequently affects the extremities and back and chest areas. Fever can accompany vaso-occlusive crisis in some patients. Although pain in patients with SCD is likely to be due to VOC, it is prudent to perform a thorough evaluation for other life-threatening causes that can

be misattributed to sickle cell pain. There is no objective measure or lab test to determine the quality and severity of pain in SCD, and therefore, patient report is the only available guide. (3)

Splenic Sequestration Crisis
Patients with SCD may have spleen infarction before the end of childhood. The spleen is affected due to its narrow vessels and its role as a key player in the lymphoreticular system. Splenic sequestration crisis causes acute, painful enlargement of the spleen due to intrasplenic trapping of red cells. Patients with splenic sequestration crisis may have a sudden drop in hemoglobin levels, if not treated properly, it could be a life-threatening situation. (3)

Aplastic Crisis
SCD presents with sudden pallor and weakness confirmed by rapidly dropping hemoglobin levels that are accompanied by reticulocytopenia. The usual trigger for aplastic crisis is parvovirus B19 that directly suppresses the bone marrow affecting red blood cell (RBC) production, but it can also be caused by other viral infections. The shortened lifespan of RBC in SCD results in worsening of the patient's baseline anemia, which can dip to dangerously low levels. The infection is self-limited, typically lasting 7 to 10 days. (3)

Acute Chest Syndrome (ACS)
This complication of SCD accounts for 25% of deaths and can follow vaso-occlusive crises. The trigger for ACS is frequently hypoxia due to hypoventilation of the chest caused by VOC crisis. It could also occur as a result of fat embolism originating from the distal bone in VOC. The hypoxia leads to adhesion of sickled erythrocytes to pulmonary microvasculature, setting up local hypoxia in the lungs and causing sickling of more RBCs; this sets up a vicious cycle. The presenting symptoms and signs include fever, cough, tachypnea, chest pain, hypoxia, wheeze, respiratory distress, and even failure. Any pulmonary infiltrate on chest radiography accompanied by abnormal lung findings should raise the suspicion of ACS. Affected patients can rapidly progress to worsening respiratory failure and death if not aggressively treated and monitored. (3)

Hemolytic Crisis
An acute drop in hemoglobin level marks this crisis. It is common in patients with coexistent glucose-6-phosphate dehydrogenase (G6PD) deficiency. (3)

Others
Femoral/humeral head osteonecrosis due to vaso-occlusion along with increased pressure from increased erythrocyte marrow, priapism, stroke, and renal complications are often due to vaso-occlusion. (3)

Regulatory
The U.S. Food and Drug Administration (FDA) approved crizanlizumab-tmca (Adakveo®) in 2019 to reduce the frequency of vaso-occlusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease. (1)

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for crizanlizumab-tmca (Adakveo).

Adakveo (1)
The efficacy of Adakveo was evaluated in patients with sickle cell disease (SCD) in SUSTAIN (NCT01895361), a 52-week, randomized, multicenter, placebo-controlled, double-blind study. A total of 198 patients with SCD, any genotype (HbSS, HbSC, HbS/beta^0-thalassemia, HbS/beta$^+$-thalassemia, and others), and a history of 2-10 vaso-occlusive crises (VOCs) in the previous 12 months were eligible for inclusion. Patients were randomized 1:1:1 to Adakveo 5 mg/kg (N = 67), Adakveo 2.5 mg/kg (N = 66), or placebo (N = 65) administered over a period of 30 minutes by intravenous infusion on Week 0, Week 2, and every 4 weeks thereafter for a treatment duration of 52 weeks. Randomization was stratified by patients already receiving hydroxyurea (Y/N) and by the number of VOCs in the previous 12 months (2 to 4, 5 to 10).

Patients received Adakveo (with or without hydroxyurea) and were allowed to receive occasional transfusions and pain medications (i.e., acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs], and opioids) on an as needed basis.

Patients recruited in the study had complications associated with SCD and other comorbidities including a history of acute chest syndrome (18%); pulmonary hypertension (8%); priapism (7%); psychiatric manifestations (25%) including depression and anxiety; hypertension (17%); cholelithiasis (17%). Demographic and other baseline characteristics were similar among the treatment groups (see Table 1).

Table 1. Demographics and Baseline Characteristics in SUSTAIN Study

	Adakveo 5 mg/kg (N=67)	**Placebo (N=65)**
Age (years)		
Median	29	26
Range	16, 63	16, 56
Gender, n (%)		
Male	32 (48%)	27 (42%)
Female	35 (52%)	38 (59%)
Ethnicity, n (%)		
Hispanic or Latino	20 (30%)	11 (17%)
Not Hispanic or Latino	45 (67%)	53 (82%)
Unknown	2 (3%)	1 (2%)
Race, n (%)		
Black or African American	60 (90%)	60 (92%)
White	4 (6%)	3 (5%)
Other	4 (5%)	2 (3%)

Sickle cell disease genotype, n (%)		
HbSS	47 (70%)	47 (72%)
HbSC	9 (13%)	8 (12%)
HbS/beta^0- thalassemia	3 (5%)	7 (11%)
HbS/beta$^+$- thalassemia	7 (10%)	1 (2%)
Other	1 (2%)	2 (3%)
Hydroxyurea use, n (%)		
Yes	43 (63%)	40 (62%)
No	25 (37%)	25 (39%)
Number of Vaso-occlusive crises in previous 12 months, n (%)		
2 to 4	42 (63%)	41 (63%)
5 to 10	25 (37%)	24 (37%)

HbSS: sickle cell disease (homozygous hemoglobin S); HbSC: sickle hemoglobin C disease; HbS/beta^0: sickle β0-thalassemia; HbS/beta$^+$: sickle β+-thalassemia.

Efficacy was evaluated in the SUSTAIN study by the annual rate of VOCs leading to a healthcare visit. A VOC leading to a healthcare visit was defined as an acute episode of pain with no cause other than a vaso-occlusive event that required a medical facility visit and treatment with oral or parenteral opioids, or parenteral NSAIDs. Acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility) were also considered VOCs.

Patients with SCD who received Adakveo 5 mg/kg had a lower median annual rate of VOC compared to patients who received placebo (1.63 vs. 2.98) which was statistically significant (p = 0.010). Reductions in the frequency of VOCs were observed among patients regardless of SCD genotype and/or hydroxyurea use.

Thirty-six percent (36%) of patients treated with Adakveo 5 mg/kg did not experience a VOC compared to 17% of placebo-treated patients. The median time to first VOC from randomization was 4.1 months in the Adakveo 5mg/kg arm compared to 1.4 months in the placebo.

The main efficacy results of the pivotal study, SUSTAIN, are summarized in Table 2.

Table 2. Efficacy Results from SUSTAIN Trial in Sickle Cell Disease[a]

Event	**Adakveo 5 mg/kg[b] (n=67)**	**Placebo[b] (n=65)**	**Treatment Difference Estimate[c]**
Annual rate of VOC[a]	1.63	2.98	HL = -1.01, (-2.00, 0.00)
Annual rate of days hospitalized	4	6.87	

HL: hodges-lehmann; VOC: vaso-occlusive crises.

[a] VOCs were as assessed by an independent review committee.

[b] Standard median.

[c] HL median difference (95% confidence interval [CI]).

Summary of Evidence

Based on the SUSTAIN trial submitted to the U.S. Food and Drug Administration (FDA) for approval, crizanlizumab-tmca (Adakveo®) is considered medically necessary for patients age 16 years and older with a diagnosis of sickle cell disease (SCD) and has experienced at least 2 sickle cell crises (i.e., medical facility visit for sickle cell-related pain, chest syndrome, priapism, or splenic sequestration) in the previous 12 months. Crizanlizumab-tmca is considered experimental, investigational and/or unproven for all other non- Food and Drug Administration approved indications.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03814746	A Phase III, Multicenter, Randomized, Double-blind Study to Assess Efficacy and Safety of Two Doses of Crizanlizumab Versus Placebo, With or Without Hydroxyurea/ Hydroxycarbamide Therapy, in Adolescent and Adult Sickle Cell Disease Patients With Vaso-Occlusive Crises (STAND)	259	Dec 2026
NCT04657822	An Open-label, Multi-center, Phase IV, Rollover Study for Patients With Sickle Cell Disease Who Have Completed a Prior Novartis-Sponsored Crizanlizumab Study	130	June 2031 (recruiting)
NCT03474965	A Phase 2, Multicenter, Open-Label Study to Assess Appropriate Dosing and to Evaluate Safety of Crizanlizumab, With or Without Hydroxyurea/Hydroxycarbamide, in Sequential, Descending Age Groups of Pediatric Sickle Cell Disease Patients With Vaso-Occlusive Crisis	118	Jan 2025

All trials industry sponsored.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0791

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. U.S. Food and Drug Administration. Drugs@FDA. Highlights of Prescribing Information. Adakveo® (revised June 2024). Available at: <https://www.accessdata.fda.gov> (accessed June 9, 2025).

Other:

2. NIH. Sickle Cell Disease. (Updated September 6, 2024) Available at: <https://medlineplus.gov> (accessed June 23, 2025).
3. Borhade MB, Patel P, Kondamudi NP. Sickle Cell Crisis. [Updated February 25, 2024]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Jan 2025. Available at: <https://www.ncbi.nlm.nih.gov> (accessed June 23, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
08/15/2025	Document updated with literature review. The following changes were made to Coverage: 1) Removed prior requirements specific to hydroxyurea; 2) Removed "Is not receiving concomitant Oxbryta (voxelotor) therapy" 3) Added "non-Food and Drug Administration approved" to the existing experimental, investigational and/or unproven statement. 4) No new references added; others updated.

02/15/2025	Reviewed. No changes.
03/15/2024	Document updated with literature review. Coverage unchanged. References updated.
05/01/2023	Document updated with literature review. Coverage unchanged. References updated.
12/01/2022	Reviewed. No changes.
10/01/2021	Document updated with literature review. Coverage unchanged. References updated.
03/01/2021	New medical document. Crizanlizumab-tmca (Adakveo®) may be considered medically necessary when ALL of the following criteria are met and the patient: is 16 years of age or older, AND; has a diagnosis of sickle cell disease, AND; has experienced at least 2 sickle cell crises (i.e., medical facility visit for sickle cell-related pain, chest syndrome, priapism, or splenic sequestration) in the previous 12 months, AND; is currently taking hydroxyurea, or has tried and failed or has a clinical contraindication/intolerance to hydroxyurea, AND; is not receiving concomitant Oxbryta (voxelotor) therapy. Crizanlizumab-tmca (Adakveo®) is considered experimental, investigational and/or unproven for all other indications.