

# Adakveo® (Crizanlizumab-Tmca) (for Ohio Only)

**Policy Number:** CSOH2024D0085.B

**Effective Date:** February 1, 2024

[Instructions for Use](#)

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Related Policies
None

## Application

This Medical Benefit Drug Policy only applies to the state of Ohio. Any requests for services that are stated as unproven or services for which there is a coverage or quantity limit will be evaluated for medical necessity using Ohio Administrative Code 5160-1-01.

## Coverage Rationale

Adakveo is proven and/or medically necessary to reduce the frequency of vasoocclusive crises in patients with sickle cell disease who meet all of the following criteria:<sup>1-3</sup>

- **Initial Therapy**
  - Patient is 16 years of age or older; **and**
  - Diagnosis of a sickle cell disease, including, but not limited to, homozygous hemoglobin S [HbSS], sickle hemoglobin C disease [HbSC], sickle beta<sup>0</sup> thalassemia, and sickle beta<sup>+</sup> thalassemia; **and**
  - Patient has previously experienced 2 or more sickle cell-related vasoocclusive crises within the previous 12 months; **and**
  - **One** of the following:
    - Patient is currently receiving hydroxyurea therapy; **or**
    - Patient has a history of treatment failure, intolerance, or contraindication to hydroxyurea therapy**and**
  - Patient is not receiving concomitant chronic, prophylactic blood transfusion therapy; **and**
  - Patient is not receiving concomitant Oxbraya (voxelotor) therapy; **and**
  - Adakveo is prescribed by, or in consultation with, a hematologist, or other specialist with expertise in the diagnosis and management of sickle cell disease; **and**
  - Adakveo initial dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Initial authorization will be for no more than 6 months
- **Continuation of Therapy**
  - Diagnosis of a sickle cell disease, including, but not limited to, homozygous hemoglobin S [HbSS], sickle hemoglobin C disease [HbSC], sickle beta<sup>0</sup> thalassemia, and sickle beta<sup>+</sup> thalassemia; **and**

- Patient has experienced a reduction in sickle cell-related vasoocclusive crises and/or a decrease in severity of sickle cell-related vasoocclusive crises from pretreatment baseline while on Adakveo; **and**
- Patient is not receiving concomitant chronic, prophylactic blood transfusion therapy; **and**
- Patient is not receiving concomitant Oxbraya (voxelotor) therapy; **and**
- Adakveo is prescribed by, or in consultation with, a hematologist, or other specialist with expertise in the diagnosis and management of sickle cell disease; **and**
- Adakveo maintenance dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Reauthorization will be for no more than 12 months

**Adakveo is not proven or medically necessary for the treatment of:**

- Pediatric patients less than 16 years of age with sickle cell disease
- Myelofibrosis

## Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0791	Injection, crizanlizumab-tmca, 5 mg

Diagnosis Code	Description
D57.0	Hb-SS disease with crisis
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
D57.2	Sickle-cell/Hb-C disease
D57.20	Sickle-cell/Hb-C disease without crisis
D57.21	Sickle-cell/Hb-C disease with 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, unspecified
D57.3	Sickle-cell trait
D57.4	Sickle-cell thalassemia
D57.40	Sickle-cell thalassemia without crisis
D57.41	Sickle-cell thalassemia, unspecified, with crisis
D57.411	Sickle-cell thalassemia, unspecified, with acute chest syndrome

Diagnosis Code	Description
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
D57.43	Sickle-cell thalassemia beta zero with 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
D57.45	Sickle-cell thalassemia beta plus with 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
D57.8	Other sickle-cell disorders
D57.80	Other sickle-cell disorders, without crisis
D57.81	Other sickle-cell disorders, with 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

## Background

Sickle cell disease (SCD) is the most common monogenic disorder that afflicts approximately 100,000 Americans and millions of people worldwide. SCD is an inherited group of disorders characterized by the presence of hemoglobin S (HbS), either from homozygosity for the sickle mutation in the beta globin chain of hemoglobin (HbSS) or from compound heterozygosity of a sickle beta globin mutation with another beta globin mutation (e.g., sickle-beta thalassemia). HbS polymerizes when deoxygenated, resulting in red blood cell sickling and membrane damage. These abnormalities lead to hemolysis, chronic anemia, inflammation, vaso-occlusion, pain crises, end-organ injury, and premature death. Sickle cell-related pain crises are the primary cause of health care encounters in patients with sickle cell disease.

Adakveo® (crizanlizumab-tmca) is a humanized IgG2 kappa monoclonal antibody that binds to P-selectin and blocks interactions with its ligands, including P-selectin glycoprotein ligand 1 (PSGL-1). Crizanlizumab can also dissociate preformed Pselectin/PSGL-1 complex. Binding P-selectin on the surface of the activated endothelium and platelets blocks interactions between endothelial cells, platelets, red blood cells, and leukocytes.<sup>1</sup>

## Crizanlizumab

The efficacy of crizanlizumab was evaluated in patients with sickle cell disease in SUSTAIN (NCT01895361), a 52-week, randomized, multicenter, placebo-controlled, double-blind trial. A total of 198 patients with sickle cell disease, any genotype (HbSS, HbSC, HbS/beta<sup>0</sup>-thalassemia, HbS/beta<sup>+</sup>-thalassemia, and others), and a history of 2-10 vasoocclusive crises (VOCs) in the previous 12 months were eligible for inclusion. Patients were randomized (1:1:1) to crizanlizumab 5 mg/kg (N = 67), 2.5 mg/kg (N = 66), or placebo (N = 65) administered intravenously over 30 minutes on week 0, 2, and every 4 weeks thereafter. Randomization was stratified by prior hydroxyurea (Y/N) and by the number of VOCs in the previous 12 months (2 to 4, 5 to 10). Seventy percent of patients receiving high-dose crizanlizumab had the HbSS genotype, and 63% of patients were on concomitant hydroxyurea. Additionally, 63% of patients had 2 to 4 VOCs in the previous 12 months.

The primary efficacy outcome measure was the annual rate of VOCs leading to a healthcare visit, defined as an acute episode of pain with no cause other than a vaso-occlusive event requiring a medical facility visit and 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. Secondary efficacy assessments included the annual rate of days hospitalized, the times to first and second crises, the annual rate of uncomplicated crises (defined as crises other than the acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism), the annual rate of the acute chest syndrome, and the Brief Pain Inventory questionnaire.

Patients receiving crizanlizumab, 5 mg/kg, had a lower median annual rate of VOC compared to those receiving placebo (1.63 vs. 2.98,  $p = 0.01$ ) indicating a 45.3% lower rate with high-dose crizanlizumab. Thirty-six percent of patients treated with crizanlizumab 5 mg/kg did not experience a VOC compared to 17% in the placebo arm. The median time to first VOC from randomization was 4.1 vs. 1.4 months in the crizanlizumab 5mg/kg and placebo arm, respectively.

Reductions in the frequency of VOCs were observed among patients regardless of sickle cell disease genotype, history of crisis frequency and/or hydroxyurea use. The median crisis rate per year among patients receiving concomitant hydroxyurea therapy was 32.1% lower in the high-dose crizanlizumab group compared to the placebo group. The median crisis rate per year among patients who were not receiving concomitant hydroxyurea therapy was 50% lower in the high-dose crizanlizumab group compared to the placebo group. The median crisis rate per year among patients who had had 2 to 4 crises in the previous 12 months was 43% lower in the high-dose crizanlizumab group compared to the placebo group. The median crisis rate per year among patients who had had 5 to 10 crises in the previous 12 months was 63% lower in the high-dose crizanlizumab group compared to the placebo group. The median crisis rate per year among patients with the HbSS genotype was 34.6% lower in the high-dose crizanlizumab group compared to the placebo group. The median crisis rate per year among patients without the HbSS genotype was 50.5% lower in the high-dose crizanlizumab group compared to the placebo group.

Among the secondary endpoints, the median time to the first crisis was significantly longer among patients receiving high-dose crizanlizumab than among those receiving placebo (4.07 vs. 1.38 months,  $P = 0.001$ ), as was the median time to the second crisis (10.32 vs. 5.09 months,  $P = 0.02$ ). The lower crisis frequency with high-dose crizanlizumab was evident within 2 weeks after the start of the 52-week treatment phase and was maintained throughout the study. The rate of uncomplicated crises per year was 62.9% lower in the high-dose crizanlizumab group than in the placebo group (median rate, 1.08 vs. 2.91;  $P = 0.02$ ). There was no significant difference in the median rates of days hospitalized or in change from baseline of the Brief Pain Inventory questionnaire with high-dose crizanlizumab. Additionally, in the clinical trial, acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism were rare (median rate, 0.00 in all groups), and there were no significant differences between the treatment group and placebo.

No significant differences were observed with crizanlizumab compared to placebo in markers of hemolysis, such as hemoglobin, lactate dehydrogenase, haptoglobin, reticulocytes, and indirect bilirubin.

## Hydroxyurea

The Multicenter Study of Hydroxyurea in Patients with Sickle Cell Anemia (MSH) was a randomized, double blind, placebo-controlled trial involving 299 adults with SCA who had experienced three or more VOCs in the previous year. The clinical end point of three or more documented VOCs was chosen because of earlier data documenting that people who experience pain at that frequency had markedly lower survival rates. The MSH trial demonstrated that, compared to placebo, hydroxyurea therapy

reduced the frequency of painful episodes and ACS events, as well as the need for RBC transfusions and hospitalizations. In 1998, based on the results of this trial, the U.S. Food and Drug Administration approved hydroxyurea for the treatment of clinically severe SCA in adults.

#### Summary of MSH Findings:

- Lower annual rates of pain crises (median 2.5 crises per year vs. 4.5 crises per year)
- Longer time to a first crisis on study (3.0 months vs. 1.5 months) and longer time to a second crisis (8.8 months vs. 4.6 months)
- Lower incidence of ACS (25 patients vs. 51 patients)
- Reduced need for blood transfusions (48 patients vs. 73 patients)
- Increased total hemoglobin (0.6 g/dL) and HbF (from 5.0 to 8.6 percent in the intervention group), compared with a drop in the placebo group (from 5.2 to 4.7 percent)
- Lower costs for hospitalization for pain (\$12,160 in the hydroxyurea group versus \$17,290 in the placebo group)
- Differences in the effect on mortality and stroke outcomes were not statistically significant.

## Professional Societies

### ***National Heart, Lung and Blood Institute (NHLBI) 2014 Evidence Report Recommendations for Hydroxyurea Therapy in the Management of Sickle Cell Disease***

- Educate all patients with SCA and their family members about hydroxyurea therapy (Consensus–Panel Expertise)
- In adults with SCA who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period, treat with hydroxyurea (Strong Recommendation, High-Quality Evidence)
- In adults with SCA who have sickle cell-associated pain that interferes with daily activities and quality of life, treat with hydroxyurea (Strong Recommendation, Moderate-Quality Evidence)
- In adults with SCA who have a history of severe and/or recurrent ACS, treat with hydroxyurea\* (Strong Recommendation, Moderate-Quality Evidence)
- In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life, treat with hydroxyurea (Strong Recommendation, Moderate-Quality Evidence)
- In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce SCD-related complications (e.g., pain, dactylitis, ACS, anemia) (Strong Recommendation, High-Quality Evidence for ages 9–42 months; Moderate Recommendation, Moderate-Quality Evidence for children > 42 months and adolescents)
- In adults and children with SCD who have chronic kidney disease and are taking erythropoietin, hydroxyurea therapy can be added to improve anemia (Weak Recommendation, Low-Quality Evidence)
- In females who are pregnant or breastfeeding, discontinue hydroxyurea therapy (Moderate Recommendation, Very Low-Quality Evidence)
- To ensure proper use of hydroxyurea and maximize benefits and safety, use an established prescribing and monitoring protocol (Strong Recommendation, High-Quality Evidence)
- In people with HbS beta<sup>+</sup>-thalassemia or HbSC who have recurrent sickle cell-associated pain that interferes with daily activities or quality of life, consult a sickle cell expert for consideration of hydroxyurea therapy (Moderate Recommendation, Low-Quality Evidence)
- In people not demonstrating a clinical response to appropriate doses and duration of hydroxyurea therapy, consult a sickle cell expert (Moderate Recommendation, Very Low-Quality Evidence)

## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Adakveo<sup>®</sup> (crizanlizumab-tmca) is indicated to reduce the frequency of vasoocclusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease.

The safety and efficacy of Adakveo<sup>®</sup> in pediatric patients below the age of 16 years have not been established.

## References

1. Adakveo® [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation, September 2022.
2. Ataga KI, Kutlar A, Kanter, J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med*. 2017; 376:429-39. DOI: 10.1056/NEJMoa1611770.
3. Supplement to: Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med* 2017;376:429-39. DOI: 10.1056/NEJMoa1611770.
4. Piel FB, Steinberg MH, Rees DC. Sickle Cell Disease. *N Engl J Med*. 2017; 376:1561-73. DOI: 10.1056/NEJMra1510865.
5. Kapoor S, Little JA, Pecker LH. Advances in the treatment of sickle cell disease. *Mayo Clin Proc*. 2018; 93(12):1810-1824.
6. Carden MA, Little J. Emerging disease-modifying therapies for sickle cell disease. *Haematologica*. 2019;104(9):1710-1719.
7. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med*. 1995;332(20):1317-22.
8. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of Sickle Cell Disease: Summary of the 2014 Evidence-Based Report by Expert Panel Members. *JAMA*. 2014;312(10):1033–1048.
9. <http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/>. Accessed February 13, 2023.
10. Study of Dose Confirmation and Safety of Crizanlizumab in Pediatric Sickle Cell Disease Patients. *Clinicaltrials.gov* website <https://clinicaltrials.gov/ct2/show/NCT03474965?term=crizanlizumab&draw=2&rank=1>. Accessed February 13, 2023.
11. Platform Study of Novel Ruxolitinib Combinations in Myelofibrosis Patients (ADORE). *Clinicaltrials.gov* website <https://clinicaltrials.gov/ct2/show/NCT04097821?term=crizanlizumab&draw=2&rank=8>. Accessed February 13, 2023.

## Policy History/Revision Information

Date	Summary of Changes
02/01/2024	<b>Applicable Codes</b> <ul style="list-style-type: none"><li>Added ICD-10 diagnosis codes D57.04, D57.214, D57.414, D57.434, D57.454, and D57.814</li></ul> <b>Supporting Information</b> <ul style="list-style-type: none"><li>Archived previous policy version CSOH2023D0085.A</li></ul>

## Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state (Ohio Administrative Code [OAC]), or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state (OAC), or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state (OAC), or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state (OAC), or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.