



Effective Date: 01/2020  
Last P&T Approval/Version: 04/27/2022  
Next Review Due By: 04/2023  
Policy Number: C17920-A

## Adakveo (crizanlizumab-tmca)

### PRODUCTS AFFECTED

Adakveo (crizanlizumab-tmca)

### COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines

#### 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 performing 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

#### DIAGNOSIS:

Sickle Cell Disease

#### REQUIRED MEDICAL INFORMATION:

This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review

#### A. SICKLE CELL DISEASE

1. Documented diagnosis of sickle cell disease confirmed by medical history, OR hemoglobin electrophoresis or high-performance liquid chromatography  
*NOTE: All SCD genotypes are eligible (including homozygous hemoglobin S [HbSS], sickle hemoglobin C disease [HbSC], sickle  $\beta$ 0-thalassemia [HbS $\beta$ 0-thalassemia], sickle $\beta$ +thalassemia [HbS $\beta$ +thalassemia], or other genotypes)*

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## Drug and Biologic Coverage Criteria

AND

2. Documentation member experienced at least TWO (2) vaso-occlusive crises (VOCs) or sickle pain crisis within the past 12 months as determined by medical history.

Documentation required. [ALL]

- i. Pain crisis defined as an acute onset of pain for which there is no other medically determined explanation other than vaso-occlusion OR Other complicated crises, such as acute chest syndrome, priapism, or hepatic or splenic sequestration
- AND
- ii. Each crisis required a visit to a medical facility and/or healthcare professional
- AND
- iii. Pain management was required: Documentation of opioids (oral/parenteral) prescribed, parenteral NSAIDs, or other analgesics.,

AND

3. Prescriber attests that member is NOT currently on a chronic transfusion program, or planning to undergo an exchange transfusion during treatment with Adakveo (crizanlizumab-tmca) AND Member is NOT receiving chronic anticoagulation (e.g., warfarin, heparin) therapy other than aspirin (exception: NSAIDs or prophylactic doses of anticoagulation) AND Member does NOT have a history of stroke within the past 2 years AND Adakveo (crizanlizumab-tmca) will NOT be used concomitantly with the following SCD pharmacologic therapies: Oxbryta (voxelotor) or Endari (L-glutamine oral powder)
- AND
4. Documentation of members current history of VOCs and current pain management treatment plan for evaluation of efficacy at renewal.
- AND
5. Documentation of an inadequate clinical response, intolerance, or contraindication to hydroxyurea. Documentation, including dates of trial(s) and reason for treatment failure
- AND
6. FOR MEMBERS CONCOMITANTLY RECEIVING ERYTHROPOEITIN AND/OR HYDROXYUREA: Prescriber attests for members concomitantly receiving erythropoietin or hydroxyurea: Treatment must have been prescribed for at least 6 months, with the dose stable for at least 3 months
- AND
7. FOR WOMEN OF CHILD-BEARING AGE: Documentation of a negative pregnancy test within the past 30 days AND Consultation on contraception and the risk versus benefit of Adakveo therapy

### CONTINUATION OF THERAPY:

#### A. SICKLE CELL DISEASE

1. Adherence to therapy at least 85% of the time as confirmed by Prescriber or member's claims history  
NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy
- AND
2. Absence of unacceptable adverse effects or complications from Adakveo (crizanlizumab-tmca) including severe infusion-related reactions, interference with automated platelet counts (platelet clumping)

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3. Documentation of clinical efficacy confirmed by a decrease in any of the following:  
Frequency of sickle cell pain crises AND Use of other sickle cell pain medications

### **DURATION OF APPROVAL:**

Initial authorization: 6 months; Continuation: 12 months

### **PRESCRIBER REQUIREMENTS:**

Prescribed by, or in consultation with, a board-certified hematologist or physician specializing in the treatment of Sickle Cell Disease (SCD). Submit consultation notes if applicable.

NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

### **AGE RESTRICTIONS:**

16 years of age or older

### **QUANTITY:**

5 mg/kg administered via intravenous infusion over a period of 30 minutes at week 0, week 2, and every 4 weeks thereafter: maximum limit of 5mg/kg/month maintenance

### **PLACE OF ADMINISTRATION:**

The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

**Note:** Site of Care Utilization Management Policy applies for Adakveo (crizanlizumab-tmca). For information on site of care, see

[Specialty Medication Administration Site of Care Coverage Criteria \(molinamarketplace.com\)](https://www.molinamarketplace.com/specialty-medication-administration-site-of-care-coverage-criteria)

## **DRUG INFORMATION**

### **ROUTE OF ADMINISTRATION:**

Intravenous

### **DRUG CLASS:**

Hematological Agents

### **FDA-APPROVED USES:**

Indicated to reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease.

### **COMPENDIAL APPROVED OFF-LABELED USES:**

None

## **APPENDIX**

### **APPENDIX:**

None

## **BACKGROUND AND OTHER CONSIDERATIONS**

### **BACKGROUND:**

## Drug and Biologic Coverage Criteria

### Sickle Cell Disease (SCD)

An autosomal recessive disorder that is genetically acquired from two abnormal alleles; individuals with *sickle cell trait* acquire one abnormal heterozygous allele, in contrast to SCD patients, who have two homozygous alleles

The condition causes red blood cells to become rigid and misshapen, to resemble a crescent, or sickle. Sickle-shaped red blood cells do not flow easily through the blood vessels and can cause blockages, vaso-occlusion, in different parts of the body. Episodes of vaso-occlusion are known as vaso-occlusive crises (VOCs).

1. VOCs. The hallmark of SCD are unpredictable, extremely painful events that last on average 10 days and can lead to acute complications; may result in emergency room visits and hospitalizations. Complications from vaso-occlusion constitute the most common cause of death in patients with SCD.
2. Leads to insufficient oxygen being delivered to tissues and organs, causing ischemic injuries and excruciating pain. The frequency, severity and duration of these crises vary.
3. Painful, known as pain crises, or damaging blockages, for example to the lung known as acute chest syndrome, or brain which leads to a stroke, are called acute sickle cell crises. Other complications of VOCs include blindness because of damage to the retina, skin ulcers if small blood vessels are blocked, and increased risk of infection if there is sustained damage to the spleen.
4. Other sickle cell crises are a result of severe anemia. These include splenic sequestration (the spleen gets enlarged because sickle red blood cells get trapped in the spleen), aplastic crisis (the bone marrow suddenly stops producing red blood cells because of a virus), and hemolytic crisis (increased rate of red blood cell destruction).

**Diagnosis.** Generally made via high performance liquid chromatography (HPLC), isoelectric focusing (IEF), or gel electrophoresis techniques; usually diagnosed in childhood through universal newborn screening

**Key clinical features of SCD.** A vaso-occlusive event can cause various complications, potentially resulting in permanent damage of vital organs such as the lungs, heart, kidneys, spleen, and brain. Common complications and leading causes of death are acute chest syndrome and stroke. Due to splenic dysfunction, SCD patients have a weakened immune system; they are more susceptible to infections and may need antibiotic treatment for prophylaxis. Other complications that may arise include priapism in men, pneumonia, and retinopathy.

**Sickle cell anemia (SCA).** The most severe subtype, which includes homozygous sickle cell disease (HbSS) and sickle beta<sup>0</sup> thalassemia; usually detected in neonatal screening and requires life-long treatment

The most common inherited blood disorder, affecting millions of people worldwide and approximately 100,000 individuals in the U.S.; prevalence of SCD disease varies considerably across different ethnic communities, mainly affecting people of African or African Caribbean origin, although the sickle gene is found in all ethnic groups and with incidence is 1 out of every 365 babies born (Centers for Disease Control and Prevention)

### Treatment

The goal of managing SCD is to prevent complications by reducing the incidence of sickle cell crises. By reducing the number of sickle cell events, the patient can minimize the potential long-term effects of the disease.

Current pharmacologic options for treatment of SCD include hydroxyurea and Endari (l-glutamine; Emmaus Medical Inc.)

1. **Hydroxyurea.** FDA approved approximately 20 years ago as a disease-modifying treatment for SCD. An orally administered drug that can ameliorate some of the complications of the disease in both adults and children. It is relatively well tolerated but requires routine monitoring, has to be continued indefinitely and may not offer protection against some of the long-term complications of the disease.
2. **Endari (an oral powder formulation of amino acid L-glutamate).** Approved in 2017 to reduce the acute complications of SCD in patients 5 years of age and older.
3. **Adakveo (crizanlizumab-tmca).** FDA approved November 2019. The first targeted therapy approved for sickle cell disease, specifically inhibiting selectin, a substance that contributes

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to cells sticking together and leads to vaso-occlusive crisis

4. *Chronic blood transfusion (CBT)*. CBT involves regularly scheduled blood transfusions to decrease circulating sickle cells and is a proven therapy for both primary and secondary stroke prevention in SCD. CBT is, however, associated with the potential for complications including transfusional hemosiderosis, alloimmunization, and the possibility of transfusion-associated infections.
5. *Bone marrow transplantation (BMT)*. Currently BMT is the only therapy for SCD with curative intent, which involves replacement of the diseased bone marrow with bone marrow from a healthy matched donor. BMT cures a high proportion of patients transplanted from matched sibling donors but is associated with risk of substantial short and long-term morbidity, long-term sequelae, and risk of mortality. Therefore, it is only available to a small subset of patients with SCD (children with frequent refractory pain episodes or severe complications) who have an available matched donor.
6. *Gene therapy and Gene editing*. Gene therapy is emerging as a possible cure for severe SCD; however, in early stages of research and available as a treatment option is not imminent at this time.

Adakveo (crizanlizumab-tmca)

Indicated to reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease (SCD). (FDA approved on November 15, 2019)

The first targeted therapy approved for SCD, specifically inhibiting selectin, a substance that contributes to cells sticking together and leads to VOC.

Crizanlizumab is an anti-P-selectin monoclonal antibody that blocks P-selectin. P-selectin drives the vaso-occlusive process, a painful complication of sickle cell disease that occurs when sickle-shaped red blood cells block blood flow through blood vessels. The blockade of P-selectin can prevent painful vaso-occlusion in small blood vessels and maintain blood flow.

*Pivotal Trial*. SUSTAIN (Ataga et al., 2017)

1. A multicenter, randomized, double-blind, placebo-controlled, phase 2 trial to assess the safety and efficacy of crizanlizumab, with or without hydroxyurea therapy, in patients with SCD. The primary goal of the trial was to determine the effect of crizanlizumab therapy on the rate of sickle cell-related crises during 52 weeks of treatment.
2. FDA approval based on the results of a randomized clinical trial enrolling 198 patients with SCD with a history of vaso-occlusive crisis. Patients either received crizanlizumab or a placebo. The patients treated with crizanlizumab experienced fewer health care visits for vaso-occlusive crisis annually (median annual rate of 1.63 visits), compared to patients who received a placebo (median annual rate of 2.98 visits). In addition, 36 percent of patients who received crizanlizumab did not experience vaso-occlusive crisis during the study, and it delayed the time that patients first experienced vaso-occlusive crisis after starting treatment from 1.4 months to 4.1 months.

Dosing is weight-based; the recommended dosage is 5 mg/kg by intravenous infusion over a period of 30 minutes at week 0, week 2, and every 4 weeks thereafter.

## CLINICAL EVIDENCE

Published evidence is limited to a Phase 2 trial SUSTAIN (Ataga et al., 2017) (NCT02452372)

### Phase 2 Trial

1. SUSTAIN Study to Assess Safety and Impact of SelG1 with or without Hydroxyurea Therapy in Sickle Cell Disease Patients with Pain Crises (SUSTAIN)
2. Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind, 12-Month Study to Assess Safety and Efficacy of Crizanlizumab (SelG1) with or without Hydroxyurea Therapy in Sickle Cell Disease Patients with Sickle Cell-Related Pain Crises (ClinicalTrials.gov number, NCT01895361)
3. A total of 198 patients (n=198) with any genotype of SCD (HbSS, HbSC, HbS/beta0-thalassemia, HbS/beta+-thalassemia, and others) and a history of 2-10 VOCs in the previous 12 months were eligible for inclusion.
4. Participants

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- 16 to 65 years of age with SCD of all genotypes and experienced 2 to 10 VOCs within 12 months of study enrollment
- Randomly assigned to receive intravenous infusions of Adakveo 2.5 mg/kg (n=66), Adakveo 5.0 mg/kg (n=67), or placebo (n=65). A total of 14 doses were administered over 52 weeks; loading doses were administered on day 1 and day 15, followed by maintenance doses every 4 weeks
- Concomitant use of hydroxyurea was permitted if participants were taking hydroxyurea for a minimum of 6 months prior to study enrollment, with a stable dose for at least 3 months prior to the start of the study. Initiation of hydroxyurea during the study was not allowed. Participants dependent on transfusion therapy were excluded from the study.
- Primary Outcome Measure: The annual rate of VOC. VOCs were defined as an acute episode of pain with no cause other than a vaso-occlusive event that required treatment at a medical facility with oral or parenteral narcotic agents or parenteral NSAIDs.
  - Treatment with high-dose Adakveo significantly reduced the annual median VOC rate by 45.3% compared with placebo (1.63 versus 2.98 events, respectively; P=0.01).
  - Treatment with low-dose Adakveo decreased the annual median VOC rate by 32.6% compared with placebo; however, these results were not statistically significant (2.01 versus 2.98 events, respectively; P=0.18).
- Secondary outcome measures included the annual rate of days hospitalized and the time to first and second crises.
  - The median time to the first crisis was significantly longer in the high-dose Adakveo group versus the placebo group (4.07 versus 1.38 months, respectively; P=0.001).
  - Similar results were reported for the median time to the second crisis (10.32 months for high-dose Adakveo versus 5.09 months for placebo; P=0.02).
  - There was no significant difference in median rate of days hospitalized between high-dose Adakveo and placebo. None of the secondary endpoints reported for low-dose Adakveo were statistically significant compared with placebo.

## Results

- Adakveo significantly lowered the median annual rate of VOCs to 1.63 vs 2.98 compared to placebo, which is equivalent to a 45% reduction. Reductions in the frequency of VOCs were observed among patients regardless of sickle cell disease genotype and/or hydroxyurea use. Additional results from the SUSTAIN study include:
  - a decrease of 42% in median annual rate of days hospitalized for Adakveo treated patients (4 days) versus placebo treated patients (6.87 days)
  - 36% of patients treated with Adakveo did not experience a VOC, compared to 17% of placebo-treated patients
  - the median time to first VOC was longer (4.1 months) in patients treated with Adakveo versus patients treated with placebo (1.4 months)
- Adverse events
- Adverse events that occurred in 10% or more of the patients in either active-treatment group and at a frequency that was at least twice as high as that in the placebo group were arthralgia, diarrhea, pruritus, vomiting, and chest pain.
  - Two serious adverse events (sepsis and intracranial hemorrhage) were reported in participants receiving Adakveo.
  - Three participants receiving Adakveo died; 2 in the high-dose group (acute chest syndrome; endocarditis with sepsis) and 1 in the low-dose group (acute chest syndrome, aspiration, respiratory failure, and progressive vascular congestion). The attrition rate for participants in the Adakveo groups was 22.73%; the overall attrition rate was 34.85%.

## Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by

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several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other crizanlizumab products may be misleading. The immunogenicity of Adakveo was evaluated using a validated bridging immunoassay for the detection of binding anti-crizanlizumab-tmca antibodies. In a single arm, open label multiple dose study, 0 of the 45 patients with sickle cell disease treated with Adakveo 5 mg/kg tested positive for treatment-induced anti-crizanlizumab-tmca antibodies. In a single-dose study of healthy subjects, 1 of the 61 (1.6%) evaluable subjects tested positive for a treatment-induced anti-crizanlizumab-tmca antibodies.

### CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Adakveo (crizanlizumab-tmca) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Authorization will not be granted if ANY of the following conditions apply [ANY]: Non-FDA approved indications, Hypersensitivity (e.g., anaphylaxis) to Adakveo (crizanlizumab-tmca) or any component of the formulation, Pregnancy, member on a chronic transfusion program or planning on exchange transfusion, Hemoglobin <4.0 g/dL or Receiving chronic anticoagulation therapy (e.g., warfarin, heparin) other than aspirin

### OTHER SPECIAL CONSIDERATIONS:

None

## CODING/BILLING INFORMATION

*Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement*

HCPCS CODE	DESCRIPTION
NA	

### AVAILABLE DOSAGE FORMS:

## REFERENCES

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Duration of Approval	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file