Original Effective Date: 01/2020
Current Effective Date: 08/23/2023
Last P&T Approval/Version: 07/26/2023
Next Review Due By: 07/2024
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. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. SICKLE CELL DISEASE
1. Documented diagnosis of sickle cell disease (SCD) 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 β0-thalassemia [HbSβ0-thalassemia], sickleβ+-thalassemia [HbSβ+-thalassemia], or other genotypes)
AND

2. Documentation member experienced at least TWO vaso-occlusive crises (VOCs) or sickle pain crisis within the past 12 months as determined by ALL of the following [DOCUMENTATION REQUIRED]:
    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.
    iv.

AND

3. Documentation of members current history of VOCs and current pain management treatment plan for evaluation of efficacy at renewal.
AND
4. Documentation of an inadequate clinical response, serious side effects, or contraindication to hydroxyurea. Documentation to include dates of trial(s) and reason for treatment failure.
AND
5. FOR MEMBERS CONCOMITANTLY RECEIVEING ERYTHROPOEITIN AND/OR HYDROXYUREA: Prescriber attests treatment has been prescribed for at least 6 months, with the dose stable for at least 3 months
AND
6. FOR WOMEN OF CHILD-BEARING AGE: Prescriber attests to a negative pregnancy prior to initiating therapy 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
AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity (e.g., severe infusion-related reactions, interference with automated platelet counts [platelet clumping])
AND
3. Documentation of clinical efficacy confirmed by a decrease in any of the following: Frequency of sickle cell pain crises OR Use of other sickle cell pain medications

DURATION OF APPROVAL:

Initial authorization: 6 months; Continuation of therapy: 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). [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

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 every 4 weeks 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)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous

DRUG CLASS:
Hematological Agents – Selectin Blockers

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:
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^0 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 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 aged16

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 12months were eligible for inclusion.
4. Participants
    - 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 by45.3% 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 (2.01versus 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 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 45patients 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.

Managing Acute Pain if You Have Sickle Cell Disease (CDC, 2022)

Know your options for treating pain. Opioids are commonly used to manage moderate to severe pain, but some patients may have acute pain that does not respond to these medicines. Talk to your provider about options that you can take instead of, or in addition to, opioids. Ketamine, an anesthetic generally used for surgery, can also help treat SCD-related acute pain. Nonmedication options for pain management include the following: Massage. Yoga. Transcutaneous electrical nerve stimulation (TENS; use of electric currents to treat pain). Virtual reality. Guided audiovisual relaxation.

American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain (ASH, 2020)

For adults and children with acute pain related to SCD, the ASH guideline panel suggests a short course (5 to 7 days) of nonsteroidal anti-inflammatory drugs (NSAIDs) in addition to opioids for acute pain management (conditional recommendation based on very low certainty in the evidence about effects)

For adults and children presenting with acute pain related to SCD who are hospitalized, the ASH guideline panel suggests a subanesthetic (analgesic) ketamine infusion as adjunctive treatment of pain that is refractory or not effectively treated with opioids alone (conditional recommendation based on very low certainty in the evidence about effects)

For adults and children presenting with acute pain related to SCD, the ASH guideline panel suggests regional anesthesia treatment approaches for localized pain that is refractory or not effectively treated with opioids alone (conditional recommendation based on very low certainty in the evidence about effects)

For adults and children who seek treatment of acute pain, the ASH guideline panel suggests massage, yoga, transcutaneous electrical nerve stimulation (TENS), virtual reality (VR), and guided audiovisual (AV) relaxation **in addition to standard pharmacological management** (conditional recommendation based on very low certainty in the evidence about effects)

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Adakveo (crizanlizumab-tmca) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Adakveo (crizanlizumab-tmca) include: No labeled contraindications.

OTHER SPECIAL CONSIDERATIONS:
Based on data from animal studies, Adakveo has the potential to cause fetal harm when administered to a pregnant woman. In an animal reproduction study, intravenous administration of crizanlizumab-tmca to pregnant cynomolgus monkeys from the onset of organogenesis through delivery resulted in a non-dose related increased fetal loss (abortions/stillbirths) at doses approximately 2.8 times the exposure at the recommended clinical dose at 5 mg/kg/dose once every 4 weeks (see Data). There are insufficient human data on Adakveo use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Advise pregnant women of the potential risk to a fetus. Adakveo should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

If a dose is missed, administer Adakveo as soon as possible. If Adakveo is administered within 2 weeks after the missed dose, continue dosing according to the patient's original schedule. If Adakveo is administered more than 2 weeks after the missed dose, continue dosing every 4 weeks thereafter.

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
J0791	Injection, crizanlizumab-tmca, 5 mg

AVAILABLE DOSAGE FORMS:
Adakveo SOLN 100MG/10ML single-dose vial

REFERENCES

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Duration of Approval Quantity Drug Class Background Contraindications/Exclusions/Discontinuation Other Special Considerations References	Q3 2023
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