Adakveo (crizanlizumab-tmca)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Adakveo is indicated to reduce the frequency of vasoocclusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease.

POLICY

Required Documentation
Submission of the following information is necessary to initiate the prior authorization review:

A. Initial therapy requests
    1. Documentation of baseline incidence of vasoocclusive crises
    2. Documentation of treatment failure, intolerance or contraindication to hydroxyurea if not currently receiving hydroxyurea
B. Continuation of therapy requests
    1. Documentation supporting the clinical benefit of Adakveo therapy (i.e., reduction in the frequency of vasoocclusive crises or the maintenance of the reduction of vasoocclusive crises, since initiating therapy with Adakveo)
    2. Documentation of treatment failure, intolerance or contraindication to hydroxyurea if not currently receiving hydroxyurea

Criteria for Initial Approval

A. Adakveo (crizanlizumab-tmca) may be considered medically necessary to reduce the frequency of vasoocclusive crises in members with sickle cell disease when the following criteria are met:
   1. The member is 16 years of age or older
   2. The member has a diagnosis of sickle cell disease of any genotype, including, but not limited to, homozygous hemoglobin S [HbSS], sickle hemoglobin C disease [HbSC], sickle beta^0 thalassemia, and sickle beta$^+$ thalassemia
   3. Adakveo is prescribed by, or in consultation with, a hematologist, or other specialist with expertise in the diagnosis and management of sickle cell disease
   4. The member has previously experienced 2 or more sickle cell-related vasoocclusive crises within the previous 12 months as determined by medical documentation
   5. The member is currently receiving and will continue to receive hydroxyurea in conjunction with Adakveo; OR the member has a documented history of treatment failure, intolerance or contraindication to hydroxyurea
   6. Adakveo will not be used in conjunction with Oxbryta (voxelotor)

Approval will be for **6 months**

Continuation of Therapy

A. Continued treatment with Adakveo (crizanlizumab-tmca) may be considered medically necessary to reduce the frequency of vasoocclusive crises in members with sickle cell disease when the following criteria are met:
   1. The member has a diagnosis of a sickle cell disease, including, but not limited to, homozygous hemoglobin S [HbSS], sickle hemoglobin C disease [HbSC], sickle beta^0 thalassemia, and sickle beta$^+$ thalassemia
   2. Adakveo is prescribed by, or in consultation with, a hematologist, or other specialist with expertise in the diagnosis and management of sickle cell disease
   3. The member has experienced a positive clinical benefit to Adakveo therapy as evidenced by a documented reduction in the frequency of vasoocclusive crises since baseline, or has maintained such reduction, since initiating therapy with Adakveo.
   4. The member is currently receiving hydroxyurea; OR the member has a documented history of treatment failure, intolerance or contraindication to hydroxyurea
   5. Adakveo will not be used in conjunction with Oxbryta (voxelotor)

Approval will be for **12 months**

Dosage and Administration
Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

CLINICAL RATIONALE

Sickle cell disease (SCD) is an autosomal recessive genetic disorder characterized by the presence of hemoglobin S (HbS) (i.e., sickle hemoglobin), which results from substitution of the amino acid valine for glutamic acid at the sixth position of the beta globin chain. This mutation causes red blood cells (RBCs) to develop a sickled (i.e., crescent) shape, which leads to clinical signs and symptoms. The hallmarks of SCD are hemolytic anemia and recurrent pain episodes (i.e., sickle cell-related pain crises or vasoocclusive crises [VOCs]), and patients may experience organ dysfunction and premature death.

Adakveo (crizanlizumab-tmca) is a selectin blocker approved by the FDA to reduce the frequency of vasoocclusive crises (VOCs) in adults and pediatric patients 16 years of age and older with sickle cell disease. Adakveo (crizanlizumab-tmca) is the first targeted therapy approved for sickle cell disease. Adakveo (crizanlizumab-tmca) is a selectin blocker humanized IgG2 kappa monoclonal antibody that binds to P-selectin and blocks interactions with its ligands including P-selectin glycoprotein ligand 1. Binding P-

selectin on the surface of the activated endothelium and platelets blocks interactions between endothelial cells, platelets, red blood cells, and leukocytes.

Efficacy

The efficacy of Adakveo (crizanlizumab-tmca) in reducing the frequency of vasoocclusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease was evaluated in the SUSTAIN trial, which was a 52-week, randomized, multicenter, placebo-controlled, double-blind, phase II trial. A total of 198 patients with sickle cell disease of any genotype and a history of 2-10 vasoocclusive crises (VOCs) in the previous 12 months were eligible for inclusion. Patients who were undergoing long-term red-cell transfusion therapy were excluded from the study. 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. Patients who were receiving concomitant hydroxyurea as well as those not receiving hydroxyurea were included in the study. Patients receiving hydroxyurea at study entry had to have been taking the drug for at least 6 months and on a stable dose for at least the most recent 3 months. Hydroxyurea could not be initiated during the trial for patients not receiving the drug at study entry. Of note, greater than 70% of patients had the homozygous hemoglobin S (HbSS) genotype and 62% of patients received concomitant hydroxyurea. In addition, 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 vasoocclusive 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 placebo (1.63 vs. 2.98, p=0.01) indicating a 45.3% lower rate of VOC with the higher dose of crizanlizumab. Patients receiving crizanlizumab 2.5mg/kg, had a 32.6% lower rate of VOC compared to placebo (2.01 vs. 2.98) but was not statistically significant. The median time to the first crisis was significantly longer with high-dose crizanlizumab than with 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. Additionally, a total of 24 of 67 patients (36%) in the high-dose crizanlizumab group, 12 of 66 (18%) in the low-dose crizanlizumab group, and 11 of 65 (17%) in the placebo group had a crisis rate of zero during the treatment phase.

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 1.00 in the high-dose crizanlizumab group, as compared with 2.00 in the placebo group (indicating a 50.0% lower rate with high-dose crizanlizumab). The median crisis rate per year among patients who had had 2 to 4 crises in the previous 12 months was 1.14 in the high-dose crizanlizumab group, as compared with 2.00 in the placebo group (indicating a 43.0% lower rate with high-dose crizanlizumab). The median crisis rate per year among patients who had had 5 to 10 crises in the previous 12 months was 1.97 in the high-dose crizanlizumab group, as compared with 5.32 in the placebo group (indicating a 63.0% lower rate with high-dose crizanlizumab). The median crisis rate per year among patients with the HbSS genotype was 1.97 in the high-dose crizanlizumab group, as compared with 3.01 in the placebo group (indicating a 34.6% lower rate with high-dose crizanlizumab). The median crisis rate per year among patients with genotypes other than HbSS (i.e., those with HbSC, HbSβ0-thalassemia, HbSβ+-thalassemia, and other genotypes) was 0.99 in the high-dose crizanlizumab group, as compared with 2.00 in the placebo group (indicating a 50.5% lower rate with high-dose crizanlizumab).

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

Reductions in the frequency of VOCs were observed in a subgroup analysis of the primary endpoint (annual rate of VOCs) with crizanlizumab 5mg/kg vs. placebo regardless of sickle cell disease genotype, the number of prior VOC events and/or concomitant hydroxyurea. Kutlar A et al. completed a post hoc analysis to further evaluate different endpoints in these same subgroups, including the proportion of patients who did not experience a VOC during the study, additional secondary efficacy endpoints and the safety of crizanlizumab 5 mg/kg compared with placebo. Further analyses of secondary endpoints demonstrated that more patients were VOC event-free in the crizanlizumab 5 mg/kg arm than in the placebo arm, including those with more frequent prior VOCs (i.e., 5-10; 28.0% vs 4.2%), the HbSS genotype (31.9% vs 17.0%) and/or using concomitant hydroxyurea (33.3% vs 17.5%). In addition, crizanlizumab treatment significantly increased time-to-first VOC vs placebo in these subgroups. Authors concluded that this post hoc analysis of SUSTAIN showed that in patients with a high number of prior VOCs, on concomitant hydroxyurea and/or with the HbSS genotype, crizanlizumab treatment increases the likelihood of patients being VOC event-free and delays time-to-first VOC.

Safety

Adakveo (crizanlizumab-tmca) may cause infusion-related reactions, and therefore patients should be monitored for signs and symptoms (i.e., fever, chills, nausea, vomiting, fatigue, dizziness, pruritus, urticaria, sweating, shortness of breath or wheezing) and treatment should be discontinued if severe reactions occur. In the SUSTAIN trial, 2 (3%) patients experienced an infusion-related reaction. Adakveo (crizanlizumab-tmca) may also interfere with automated platelet counts, particularly when blood samples are collected in tubes containing ethylenediaminetetraacetic acid (EDTA), which may lead to unevaluable or falsely decreased platelet counts. Blood samples should be run within 4 hours of blood collection or blood samples should be collected in tubes containing citrate. Adakveo (crizanlizumab-tmca) is generally well-tolerated, but is associated with nausea (18%), arthralgia (18%), back pain (15%), and pyrexia (11%).

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- C9053 Injection, crizanlizumab-tmca, 1 mg
- J3490 Unclassified drugs
- J3590 Unclassified biologics

REFERENCES

- Adakveo [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; November 2019.
- 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(5):429-439.
- Kutlar A, Kanter J, Liles DK, et al. Effect of Crizanlizumab on pain crises in subgroups of patients with sickle cell disease: A SUSTAIN study analysis. Am J Hematol. 2019;94:55-61.
- U.S. Food and Drug Administration (FDA). FDA approves first targeted therapy to treat patients with painful complication of sickle cell disease. Silver Spring, MD: FDA; November 15, 2019.

POLICY HISTORY

Policy #: 05.03.97
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