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Subject: Crizanlizumab-tcma (Adakveo)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Sickle cell disease (SCD) represents a group of inherited disorders carried by the beta allele of the hemoglobin (Hb) gene. It is characterized by abnormal hemoglobin polymerization that results in a sickle-shaped erythrocyte. This sickled alteration results in a shortened lifespan of the erythrocyte (16 days vs 120 days in normal RBCs) and ultimately results in vascular occlusion.

The term SCD includes the homozygous genotype HbSS and the heterozygous genotypes HbSβ^0 thalassemia, HbSC, HbSD, and HbSβ+ thalassemia. An individual with one normal gene and one HbS gene (HbAS) is a carrier and referred to as “sickle cell trait”. Sickle cell trait typically does not have clinical manifestations of the disease.

Acutely, patients with SCD present with recurrent pain episodes, life-threatening infections due to splenic infarction, acute chest syndrome, pulmonary hypertension, stroke, and cumulative multiorgan damage. These episodes are categorized as vaso-occlusive crises (VOCs). Treatment options for SCD predominantly focus on management of symptoms and secondary complications and include hydroxyurea, L-glutatmine, and blood transfusions. The only curative option is hematopoietic cell transplantation.

Crizanlizumab-tcma (Adakveo) was approved by the U.S. Food and Drug Administration (FDA) in November 2019 for the treatment of the treatment of sickle cell disease in adults and pediatric patients 16 years of age and older. Crizanlizumab-tcma, a humanized IgG2 kappa monoclonal antibody, inhibits adhesion of sickled red blood cells by binding to P-selectin and preventing interaction with P-selectin glycoprotein ligand 1. Binding P-selectin on the surface of activated endothelium and platelets blocks interactions between endothelial cells, platelets, red blood cells, and leukocytes.

The safety and efficacy of crizanlizumab-tcma were evaluated in a phase II, placebo-controlled trial (SUSTAIN). Individuals with SCD were randomized to receive 5.0 mg/kg of crizanlizumab (n=67) or placebo (n=65). The trial included a 30-day screening phase, a 52-week treatment phase, and a 6-week follow-up evaluation phase. Crizanlizumab was administered intravenously in two loading doses, two weeks apart, and every 4 weeks thereafter through week 50 of the trial (14 total doses).

Patients 16-65 years of age were eligible to participate in SUSTAIN if they had any genotype of SCD and experienced 2-10 SCD-related acute pain crises in the 12 months prior to enrollment. Patients who had been receiving treatment with hydroxyurea for at least 6 months and had maintained a stable dose during

the 3 months immediately preceding enrollment, were permitted to continue therapy during the trial; receipt of chronic red-cell transfusions was an exclusion criterion.

Patients in the crizanlizumab group had a median age of 29 years, 52% were females, 90% were black, 70% had an HbSS SCD genotype, and 63% were receiving concomitant therapy with hydroxyurea. The proportion of patients with 2-4 or 5-10 SCD-related crises in the previous year, was 63% and 37%, respectively.

The primary endpoint was the annual rate of sickle cell-related pain crises, defined as acute episodes of pain, with no medically determined cause other than a vaso-occlusive event, that resulted in a medical facility visit and treatment with oral or parenteral narcotic agents or with a parenteral nonsteroidal anti-inflammatory drug. Acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility) were also considered to be crisis events.

Compared to optimal usual care alone (i.e., placebo), patients treated with crizanlizumab experienced fewer acute pain crises per year and sustained a longer period of time before the first (and second) crises following initiation of the trial therapy. The median annualized crisis rate was 1.63 in the crizanlizumab group and 2.98 in the placebo group (median difference -1.01, p=0.01).

The median rate of days hospitalized per year was 4.0 (IQR 0.0-25.7) in the crizanlizumab group and 6.9 (IQR 0.0-28.3) in the placebo group; this difference did not reach statistical significance. A post-hoc time to event analysis also did not reach statistical significance but suggested that crizanlizumab may have delayed time to first hospitalization (median 6.3 vs. 3.2 months for the crizanlizumab and placebo arms, respectively; HR 0.68 [95% CI 0.44 to 1.07]).

There were three deaths among patients treated with crizanlizumab, although none were considered by the investigator to be related to the study therapy. The rate of discontinuation due to an AE was low. The most commonly reported AEs included back pain, nausea, arthralgia, and pyrexia.

The Institute for Clinical and Economic Review (ICER) will release a final evidence report in April 2020 to assess the comparative clinical effectiveness and value of treatments in sickle cell disease.

POSITION STATEMENT:

Initiation of crizanlizumab-tcma (Adakveo) **meets the definition of medical necessity** when all of the following criteria are met:

1. Indication for use is sickle cell disease (SCD) – documentation from the medical record must be provided
2. Member has experienced a minimum of two sickle cell-related pain crises requiring hospitalization in the past 12 months – documentation from the medical record must be provided
3. Member meets one of the following:
    a. Member is currently receiving a hydroxyurea product
    b. Member has a history of treatment failure, intolerance, or contraindication to hydroxyurea therapy
4. Treatment is prescribed by or in consultation with a board certified (or board eligible) hematologist
5. Member is not concurrently enrolled in a clinical trial to receive an experimental therapy for SCD
6. Dose does not exceed the following:
    a. Initial: 5 mg/kg at week 0 and week 2
    b. Maintenance: 5 mg/kg every 4 weeks beginning at week 6

Approval duration: 6 months

Continuation of crizanlizumab-tcma (Adakveo) **meets the definition of medical necessity** when all of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue in the past two years for treatment of sickle cell disease (SCD), **OR** the member has previously met all indication-specific initiation criteria
2. Member has demonstrated a beneficial response to treatment with crizanlizumab as evidenced by a reduction in the number of sickle cell-related pain crises – documentation from medical record must be provided
3. Treatment is prescribed by or in consultation with a board certified (or board eligible) hematologist
4. Member is not concurrently enrolled in a clinical trial to receive an experimental therapy for SCD
5. Dose does not exceed 5 mg/kg every 4 weeks

Approval duration: 6 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- 5 mg/kg by intravenous infusion over a period of 30 minutes at Week 0, Week 2, and every 4 weeks thereafter

Dose Adjustments

- 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.

Drug Availability

- Injection: 100 mg/10 mL (10 mg/mL) solution in a single-dose vial

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- Infusion-Related Reactions: Monitor patients for signs and symptoms. Discontinue for severe reactions and manage medically.
- Interference With Automated Platelet Counts (platelet clumping): Run test as soon as possible or use citrate tube

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J0791	Injection, crizanlizumab-tmca, 5 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

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
D57.04	Hb-SS disease with dactylitis
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
D57.214	Sickle-cell/Hb-C disease with dactylitis
D57.219	Sickle cell/Hb-C disease with crisis, unspecified
D57.41	Sickle cell thalassemia with crisis
D57.411	Sickle cell thalassemia with acute chest syndrome
D57.412	Sickle cell thalassemia with splenic sequestration
D57.414	Sickle-cell thalassemia, unspecified, with dactylitis
D57.419	Sickle cell thalassemia with crisis, unspecified
D57.434	Sickle-cell thalassemia beta zero with dactylitis
D57.454	Sickle-cell thalassemia beta plus with dactylitis
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
D57.814	Other sickle-cell disorders with dactylitis
D57.819	Other sickle cell disorders with crisis unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

DEFINITIONS:

Acute Hepatic Sequestration: patients with hepatic sequestration usually present with right upper quadrant pain, rapidly increasing hepatomegaly, and a falling hematocrit.

Acute Kidney Injury/Renal Infarction: a condition resulting from a sudden disruption of blood flow to the renal artery. This may cause irreversible damage to kidney tissues.

Chronic Kidney Disease (Nephropathy): defined in trials as either having a glomerular filtration rate (GFR) of less than 60ml/min/1.73 m2 for greater than or equal to 3 months with or without kidney damage

or having evidence of kidney damage for greater than or equal to 3 months, with or without decreased GFR, manifested by either pathologic abnormalities or markers of kidney damage independent of cause.

Chronic Sickle Cell Pain: pain that does not resolve and lasts for more than 3 months.

HbSβ0 thalassemia: occurs in patients who inherit one sickle cell gene and one beta thalassemia gene that results in no production of HbA.

HbSβ+ thalassemia: occurs in patients who inherit one sickle cell gene and one beta thalassemia gene resulting in reduced production of HbA.

HbSC: sickle cell hemoglobin C disease

HbSD, HbSE and HbSO22: one inherited sickle cell gene (“S”) and one gene from an abnormal type of hemoglobin (“D”,“E” or “O”).

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, Friedrisch J, Guthrie TH, Knight-Madden J, Alvarez OA, Gordeuk VR, Gualandro S, Colella MP, Smith WR, Rollins SA, Stocker JW, Rother RP: Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med. 2017 Feb 2;376(5):429-439.
2. Brown C, Hoppe C, Inati A, et al. Efficacy and Safety of 1500 mg Voxelotor in a Phase 2a Study (GBT440-007) in Adolescents with Sickle Cell Disease. Blood:132(Suppl 1):509.
3. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2026 [cited 4/1/26]. Available from: http://www.clinicalpharmacology.com/.
4. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 4/1/26]. Available from: http://clinicaltrials.gov/.
5. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 4/1/24].
6. Novartis. Adakveo (crizanlizumab) injection. 2026 [cited 4/1/26]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b2b7f8b4-fe9a-4a86-8129-9e43f99a20c6.
7. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2026 [cited 4/1/26]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/08/26.

GUIDELINE UPDATE INFORMATION:

03/15/20	New Medical Coverage Guideline.
04/01/20	HCPCS Update: Added code C9053.

07/01/20	Revision: Added HCPCS code J0791 and deleted codes C9053 and J3590.
07/15/21	Review and revision of guideline; Updated references.
05/15/22	Review and revision of guideline; Updated references.
10/01/23	Revision to guideline; ICD10 code update.
05/15/24	Review and revision of guideline; Updated position statement and references.
05/15/26	Review and revision of guideline; Updated position statement and references.