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Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

**Effective Date: 12/14/2023**

**Adakveo® (crizanlizumab-tmca)**

**HCPCS: J0791**

**Policy:**

*Requests must be supported by submission of chart notes and patient specific documentation.*

- A. Coverage of the requested drug is provided when all the following are met:
  - a. FDA approved indication
  - b. FDA approved age
  - c. Prescribed by or in consultation with a hematologist
  - d. Patient has experienced 2 or more sickle cell-related crises in the past 12 months
  - e. Trial and failure for at least 6 months, contraindication, OR intolerance to hydroxyurea
  - f. Must not be using long-term red blood cell transfusion therapy
  - g. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list
  
- B. Quantity Limitations, Authorization Period and Renewal Criteria
  - a. Quantity limit: Align with FDA recommended dosing
  - b. Initial Authorization Period: One year at a time
  - c. Renewal Criteria: Patient has experienced a decrease in the number of sickle cell-related crises

\*\*\*Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at <http://www.cms.hhs.gov/>. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

**Background Information**

- Sickle cell disease (SCD) is a recessive hemolytic anemia caused by a mutation in the  $\beta$ -globin gene. It is characterized by the formation of sickle hemoglobin (HbS). HbS is less soluble and less elastic than fetal hemoglobin (HbF) or normal adult hemoglobin (HbA). The disease involves multicellular adhesion between sickled red blood cells, white blood cells, platelets, and endothelial cells resulting in vaso-occlusive crises (VOCs). VOCs are the hallmark of SCD and are experienced by approximately 70% of patients. They are recurring, unpredictable, painful events that decrease organ function with complications including stroke, pneumonia, vision loss, pulmonary

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hypertension, leg ulcers, and sepsis. VOCs are often treated as an emergency requiring acute care and are the number one reason patients with SCD visit the emergency room or are hospitalized.

- Hydroxyurea is a ribonucleotide reductase inhibitor which increases the amount of circulating HbF in the body and has been a mainstay of therapy. It also has been shown to lower the number of circulating leukocytes and reticulocytes altering the expression of adhesion molecules; raise red blood cell (RBC) volume; and improve cellular deformability and rheology, all of which contribute to a decrease in VOCs. The 2014 National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease Guidelines recommend the use of hydroxyurea for the following patient populations:
  - In adults with SCD who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period
  - In adults with SCD who have sickle cell-associated pain that interferes with daily activities and quality of life
  - In adults with SCD who have a history of severe and/or recurrent acute coronary syndrome
  - In adults with SCD who have severe symptomatic chronic anemia that interferes with daily activities or quality of life
  - In infants 9 months of age and older, children, and adolescents with SCD, offer treatment with hydroxyurea regardless of clinical severity to reduce complications
  - In adults and children with SCD who have chronic kidney disease and are taking erythropoietin
- The guidelines recommend starting hydroxyurea at a dose of 15 mg/kg/day for adults and increasing the dose by 5 mg/kg/day every 8 weeks to a maximum dose of 35 mg/kg/day. A clinical response to therapy may take 3 – 6 months. Therefore, a 6 month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.
- Adakveo is a monoclonal antibody that is indicated to reduce the frequency of VOCs in adults and pediatric patients aged 16 years and older with sickle cell disease. It binds to P-selectin and blocks interactions between endothelial cells, platelets, RBCs, and leukocytes. P-selectin plays a role in the formation of the multicellular aggregates that lead to VOCs.
- The efficacy of Adakveo was evaluated in the SUSTAIN trial, a randomized, multicenter, placebo-controlled, double-blind trial of 198 patients with sickle cell disease of any genotype and a history of 2 - 10 VOCs in the previous 12 months. Patients were excluded if they were receiving long-term red blood cell transfusions. The primary endpoint was the annual rate of VOCs leading to a healthcare visit. Acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility) were also considered VOCs. Patients receiving Adakveo 5 mg/kg, had a lower median annual rate of VOC compared to those receiving placebo (1.63 vs. 2.98, p-value = 0.01) indicating a 45.3% lower rate with Adakveo. Thirty-six percent of patients treated with Adakveo did not experience a VOC compared to 17% in the placebo arm. The median time to first VOC from randomization was 4.1 months vs. 1.4 months in the Adakveo and placebo arm, respectively.

## References:

1. Adakveo [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; September 2022.
2. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *New Engl J Med.* 2017; 376 (5): 429 – 439.
3. Ogedegbe HO. Sickle cell disease: an overview. *Laboratory Medicine.* 2002; 33(7): 515 – 543.

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4. Yale SH, Nagib N, & Guthrie T. Approach to the vaso-occlusion crisis in adults with sickle cell disease. Am Fam Physician. 2000; 61(5): 1349 – 1356.
5. Kanter J & Kruse-Jarres R. Management of sickle cell disease from childhood through adulthood. Blood Rev. 2013; 27(6): 279 – 287.
6. Brousseau DC, Panepinto JA, Nimmer M, et al. The number of people with sickle-cell disease in the United States: national and state estimates. Am J Hematol. 2010; 85(1): 77 – 78.
7. National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease: expert panel report, 2014. Available at: <https://www.nhlbi.nih.gov/sites/default/files/publications/56-364NFULL.pdf>. Accessed on: October 4, 2020.

Policy History												
#	Date	Change Description										
1.7	Effective Date: 12/14/2023	Annual review of criteria was performed, no changes were made										
1.6	Effective Date: 12/01/2022	Annual review of criteria was performed, no changes were made										
1.5	Effective Date: 12/09/2021	Annual review of criteria was performed, no changes were made										
1.4	Effective Date: 12/03/2020	Updated to include a trial and failure of hydroxyurea, the trial and failure of preferred products statement, and updated the approval duration to 1 year										
1.3	Effective Date: 03/16/2020	UM medical management system update for MAPPO and BCNA <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>Yes</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>Yes</td> </tr> <tr> <td>BCNA</td> <td>Yes</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	Yes	BCNA	Yes
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1.2	Effective Date: 02/01/2020	UM medical management system update for BCBS <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>Yes</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>No</td> </tr> <tr> <td>BCNA</td> <td>No</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	No	BCNA	No
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1.0	Effective Date: 12/05/2019	New full drug review										

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*\* The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or <http://dailymed.nlm.nih.gov/dailymed/index.cfm>.*