Oscar Clinical Guideline: Adakveo (crizanlizumab) (PG193, Ver. 1)

Adakveo (crizanlizumab)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Sickle cell disease (SCD) is an inherited blood disorder caused by mutations in the beta-globin gene, resulting in production of abnormal hemoglobin S that polymerizes under deoxygenated conditions, causing red blood cells to become sickle-shaped. This leads to vaso-occlusion, hemolysis, and endothelial dysfunction, causing acute complications like painful vaso-occlusive crises (VOCs), acute chest syndrome (ACS), and stroke, as well as chronic organ damage. Standard treatment includes hydroxyurea to increase fetal hemoglobin, red blood cell transfusions, and more recently, targeted therapies like voxelotor and crizanlizumab. However, many patients continue to experience recurrent severe crises despite available therapies. Allogeneic hematopoietic stem cell transplant (HSCT) can be curative but is limited by donor availability and transplant-related risks.

Adakveo (crizanlizumab), administered as a monthly intravenous infusion, is a humanized IgG2 monoclonal antibody developed by Novartis for the prevention of VOCs in patients with SCD. It works

by binding to P-selectin, a cell adhesion protein that plays a key role in the pathogenesis of VOCs. By inhibiting P-selectin, Adakveo (crizanlizumab) aims to reduce the frequency of these painful episodes.

Adakveo (crizanlizumab) received FDA approval in November 2019 based on the results of the phase 2 SUSTAIN trial[3] (NCT01895361), which showed a significant reduction in the annual rate of VOCs compared to placebo. However, the drug's efficacy and safety have been called into question following the recent phase 3 STAND trial[1] (NCT03814746), which failed to demonstrate superiority over placebo in reducing VOCs. In August 2023, the European Medicines Agency (EMA) revoked the conditional marketing authorization for crizanlizumab[7], citing concerns about its benefit-risk profile in light of the STAND trial[1] results.

Definitions

"**Sickle cell disease**" refers to a group of inherited blood disorders caused by a mutation in the beta-globin gene, resulting in abnormal hemoglobin S that polymerizes under deoxygenated conditions, causing red blood cells to become sickle-shaped and prone to hemolysis and vaso-occlusion, leading to a complex pathophysiology involving chronic inflammation, endothelial dysfunction, and end-organ damage.

"**Vaso-occlusive crisis**" refers to the hallmark acute complication of sickle cell disease caused by obstruction of blood flow in the microcirculation by sickled red blood cells, leading to tissue ischemia and severe pain, often requiring hospitalization for pain management, intravenous fluids, and other supportive care.

Policy Statement on Adakveo (crizanlizumab) Efficacy Information

Based on a review of the available evidence, including the FDA label, clinical trial data, treatment guidelines, and real-world data, the Plan considers Adakveo (crizanlizumab) unproven and not medically necessary for the prevention of vaso-occlusive crises (VOCs) in patients with sickle cell disease (SCD) at this time.

The pivotal phase 2 SUSTAIN trial[3] (NCT01895361) showed a statistically significant reduction in VOCs with high-dose crizanlizumab compared to placebo. However, the confirmatory phase 3 STAND trial[1] (NCT03814746) failed to demonstrate superiority of either crizanlizumab 5 mg/kg or 7.5 mg/kg over placebo in reducing VOCs leading to healthcare visits or managed at home. The lack of benefit seen in

STAND[1], a larger and more robust study, suggests Adakveo (crizanlizumab) may not provide a clinically meaningful benefit.

Additionally, real-world data on the use of Adakveo (crizanlizumab) is limited but concerning. One single-center study found that while Adakveo (crizanlizumab) decreased acute care visits for VOCs in high utilizers, the discontinuation rate was extremely high, with only 1 out of 9 patients remaining on treatment by the end of the study period. Reasons for discontinuation included inability to adhere to monthly infusion appointments, perceived lack of efficacy, worsening of pain, and lack of transportation. These findings raise doubts about the real-world effectiveness and feasibility of Adakveo (crizanlizumab).

There are also unanswered questions regarding the long-term efficacy and safety of Adakveo (crizanlizumab). The SUSTAIN trial[3] only lasted 52 weeks, which is considered short for evaluating the impact on outcomes in a chronic disease like SCD. The effect of chronic blockade of P-selectin is unknown. Serious adverse events such as infections and infusion-related reactions have been reported.

Medical Necessity Criteria for Adakveo (crizanlizumab)

Evidence is insufficient to conclude that Adakveo (crizanlizumab) provides a clinically meaningful benefit that outweighs the risks for patients with SCD. Well-designed studies demonstrating a clear efficacy and safety advantage over existing therapies are needed. Therefore, Adakveo (crizanlizumab) is considered unproven and not medically necessary at this time. Coverage will be re-evaluated as new evidence becomes available.

Experimental or Investigational / Not Medically Necessary

Adakveo (crizanlizumab) for any indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Sickle Cell Disease (SCD)
    - The phase 3 STAND trial (n=252) failed to show a statistically significant difference in the annualized rates of VOCs leading to healthcare visits between crizanlizumab 5 mg/kg and 7.5 mg/kg vs placebo (rate ratio [RR] 1.08, 95% CI 0.76-1.55, P>.999). There was also no significant difference in the rate of VOCs managed at home or leading to healthcare visits (RR 0.83, 95% CI 0.59-1.17). These results contrast with the earlier phase

2 SUSTAIN trial and suggest crizanlizumab may not provide a clinically meaningful benefit.

- Advanced Glioblastoma / Metastatic Melanoma in the Central Nervous System / MGMT-unmethylated Glioblastoma (GBM).
- Myelofibrosis.
- Priapism.
- Retinal Vasculopathy Cerebral Leukoencephalopathy.

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name	
CPT/HCPCS Codes considered experimental or investigational or not considered medically necessary:	
Code	*Description*
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
J0791	Injection, crizanlizumab-tmca, 5 mg
C9399	Unclassified drugs or biologicals
J3590	Unclassified biologics
ICD-10 Codes considered experimental or investigational or not considered medically necessary:	
Code	*Description*
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
D57.03	Hb-SS disease with cerebral vascular involvement
D57.09	Hb-SS disease with crisis with other specified complication
D57.211	Sickle-cell/Hb-C disease with acute chest syndrome

D57.212	Sickle-cell/Hb-C disease with splenic sequestration
D57.219	Sickle-cell/Hb-C disease with crisis, unspecified
D57.411	Sickle-Cell Thalassemia, Unspecified, With Acute Chest Syndrome
D57.412	Sickle-Cell Thalassemia, Unspecified, With Splenic Sequestration
D57.419	Sickle-Cell Thalassemia, Unspecified, With Crisis
D57.811	Other sickle-cell disorders with acute chest syndrome
D57.812	Other sickle-cell disorders with splenic sequestration
D57.819	Other sickle-cell disorders with crisis, unspecified

References

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3. 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. doi:10.1056/NEJMoa1611770
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Clinical Guideline Revision / History Information

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