Oscar Clinical Guideline: Adakveo (crizanlizumab) (PG193, Ver. 2)

# 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.*

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## 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 preventative treatment includes hydroxyurea to increase fetal hemoglobin; l-glutamine, for regulating and preventing red blood cell oxidative damage; pain management, for both acute and chronic pain; red blood cell transfusions; and more recently, targeted therapies like voxelotor (which was withdrawn from the market in September, 2024) and Adakveo (crizanlizumab).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 in adults and pediatric patients aged 16 and older. 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 conflicting. 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). Another small study looked at real-world data from 2018-2023, and found that amongst 112 patients, Adakveo (crizanlizumab) there was both a reduction in home and health-care managed VOCs, a reduction in a significant reduction in opioid use.

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, ***and***
- Retinal Vasculopathy Cerebral Leukoencephalopathy.

## Applicable Billing Codes (HCPCS/CPT Codes)

| ***Service(s) name*** | |
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| **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 |
| **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 |
| D67.04 | Hb-SS disease with dactylitis |
| 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 |

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| D57.213 | Sickle-cell/Hb-C disease with cerebral vascular information. |
| D57.214 | Sickle-cell HbC disease with dactylitis |
| D57.218 | Sickle- cell/Hb disease with cerebral vascular disease |
| D57.219 | Sickle-cell/Hb-C disease with crisis, unspecified |
| D.57.40 | Sickle-cell thalaaemia without crisis |
| D57.411 | Sickle-Cell Thalassemia, Unspecified, With Acute Chest Syndrome |
| D57.412 | Sickle-Cell Thalassemia, Unspecified, With Splenic Sequestration |
| D57.413 | Sickle-cell thalassemia, unspecified, with cerebral vascular involvement |
| D57.414 | Sickle-cell thalassemia, unspecified, with dactylitis |
| D57.418 | Sickle-cell thalassemia, unspecified, with crisis with other specified complication |
| D57.419 | Sickle-Cell Thalassemia, Unspecified, With Crisis |
| D57.42 | Sickle-cell thalassemia beta zero without crisis |
| D57.431 | Sickle-cell thalassemia beta zero with acute chest syndrome |
| D57.432 | Sickle-cell thalassemia beta zero with splenic sequestration |
| D57.433 | Sickle-cell thalassemia beta zero with cerebral vascular involvement |
| D57.434 | Sickle-cell thalassemia beta zero with dactylitis |
| D57.438 | Sickle-cell thalassemia beta zero with crisis with other specified complication |
| D57.439 | Sickle-cell thalassemia beta zero with crisis, unspecified |
| D57.44 | Sickle-cell thalassemia beta plus without crisis |
| D57.451 | Sickle-cell thalassemia beta plus with acute chest syndrome |
| D57.452 | Sickle-cell thalassemia beta plus with splenic sequestration |
| D57.453 | Sickle-cell thalassemia beta plus with cerebral vascular involvement |
| D57.454 | Sickle-cell thalassemia beta plus with dactylitis |
| D57.458 | Sickle-cell thalassemia beta plus with crisis with other specified complication |
| D57.459 | Sickle-cell thalassemia beta plus with crisis, unspecified |
| D57.811 | Other sickle-cell disorders with acute chest syndrome |
| D57.812 | Other sickle-cell disorders with splenic sequestration |
| D57.813 | Other sickle-cell disorders with cerebral vascular involvement |

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| D57.814 | Other sickle-cell disorders with dactylitis |
| D57.819 | Other sickle-cell disorders with crisis, unspecified |
| H36.811 | Nonproliferative sickle-cell retinopathy, right eye |
| H36.812 | Nonproliferative sickle-cell retinopathy, left eye |
| H36.813 | Nonproliferative sickle-cell retinopathy, bilateral |
| H36.819 | Nonproliferative sickle-cell retinopathy, unspecified eye |
| H36.821 | Proliferative sickle-cell retinopathy, right eye |
| H36.822 | Proliferative sickle-cell retinopathy, left eye |
| H36.823 | Proliferative sickle-cell retinopathy, bilateral |
| H36.829 | Proliferative sickle-cell retinopathy, unspecified eye |
| O35.2XX0 | Maternal care for (suspected) hereditary disease in fetus, not applicable or unspecified |
| O99.019 | Anemia complicating pregnancy, unspecified trimester |
| P09.3 | Abnormal findings on neonatal screening for congenital hematological disorders |

## References


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## Clinical Guideline Revision / History Information

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