Adakveo (crizanlizumab)

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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and more recently, targeted therapies like voxelotor (which was withdrawn from the market in September, 2024) and Adakveo (crizanlizumab).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 (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 (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, citing concerns about its benefit-risk profile in light of the STAND trial 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.

"[s]" indicates state mandates may apply.

Policy Statement on Adakveo (crizanlizumab) Efficacy Information[s]

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 therefore not medically necessary for the prevention of vaso-occlusive crises (VOCs) in patients with sickle cell disease (SCD) at this time.

The current efficacy data for Adakveo (crizanlizumab) in Sickle Cell Disease:

- The pivotal phase 2 SUSTAIN trial (NCT01895361) showed a statistically significant reduction in VOCs with high-dose crizanlizumab compared to placebo. The SUSTAIN study (n=198) found a median crisis rate per year of 1.63 in the high-dose Adakveo (crizanlizumab) versus 2.98 in the placebo group (p=0.01); there was no difference in median crisis rate per year between the low-dose Adakveo (crizanlizumab) and placebo (p=0.18). During follow-up, 36%, 18% and 17% experience zero crises during the treatment phase in the high-dose, low-dose and placebo group, respectively. There was no significant difference in the secondary outcome of median rate of days hospitalized (4.00 versus 6.87 in the high-dose versus placebo group, respectively; p=0.45). However, the confirmatory phase 3 STAND trial (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.
- 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).
- 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 (NCT03720626) looked at real-world data from 2018-2023, and found that amongst 112 patients, Adakveo (crizanlizumab), administered at 5mg/kg, there was both a reduction in home (-3.0 median change from baseline [interquartile range -6.0, 0]) and health-care (-2.0 median change from baseline [interquartile range -4.0, -1.0]) managed VOCs, a reduction in a significant reduction in opioid use (35.5%). There was no comparator group, however, and the study sample was small.
- 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.

On-going studies (pending results):

- A roll-over study of the original parent studies noted above (NCT04657822) is currently recruiting participants.

- The SPARKLE study, a phase 3, multi-center, randomized, placebo-controlled, double-blind study assessing the safety and efficacy of crizanlizumab (5mg/kg) versus placebo in adolescents and adults with frequent VOCs is currently in the recruitment phase (NCT06439082). The estimated enrollment will be 315 participants.

Safety Considerations:

- In the SUSTAIN phase 2 study the following side effects occurred at a rate of greater than 10% in the active treatment arms were identified: headache, back pain, nausea, neuralgia, pain in upper and lower limbs, urinary tract infection, upper respiratory tract infection, pyrexia, diarrhea, musculoskeletal pain, pruritus, vomiting and chest pain.
- The STAND phase 3 trial did not identify any new or emergent adverse effects, and noted no major difference between the placebo and high-dose Adakveo (crizanlizumab) groups.
- Infusion-related reactions (IRR) occurred in 3% of participants who received Adakveo (crizanlizumab) 5 mg/lg dosing in the SUSTAIN study, while 7% experienced an IRR in the STAND study who were exposed to the same dose. IRRs present as severe pain, nausea, vomiting, fatigue, dizziness, pruritus, diarrhea and pyrexia. They can require hospitalization or emergency department visits. If an IRR occurs, it is advised to either discontinue Adakveo (crizanlizumab) in severe cases, or temporarily interrupt the infusion, slow the rate of infusion or administer symptomatic treatment in the case of mild-to-moderate IRRs. It is noted in the package insert that corticosteroids should be used sparingly in these individuals, as they may increase the risk of acute chest syndrome and fat embolisms.

Guidelines/Position Statements:

- The European Medicines Agency (EMA) revoked the marketing authorization of Adakveo (crizanlizumab) following the 2023 publication of the STAND trial results - citing lack of drug efficacy as a major contributor.
- The United Kingdom National Institute for Health Care Excellence (NICE) guidelines currently do not support the use of Adakveo (crizanlizumab) for the management of SCD.
- The Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom withdrew the Adakveo (crizanlizumab) license as of January 2024.
- The Sickle Cell Disease Association of America's Medical and Research Advisory Committee published a statement in July, 2023 stating that while the EMA has revoked the marketing authorization of Adakveo (crizanlizumab), they recommend the US FDA continue to keep the drug on market. They cite that given the lack of available drug therapies for those with SCD, no major adverse effect findings, and that preliminary studies on outcomes for priapism and renal complications have not yet been published, there is no reason to yet remove it from the US market.

Medical Necessity Criteria for Adakveo (crizanlizumab)[s]

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. Adakveo (crizanlizumab) is considered unproven and therefore not medically necessary at this time. Coverage will be re-evaluated as new evidence becomes available.

Experimental or Investigational or Unproven / Not Medically Necessary[s]

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

- Sickle Cell Disease (SCD)
- Advanced Glioblastoma / Metastatic Melanoma in the Central Nervous System / MGMT-unmethylated Glioblastoma (GBM). The National Comprehensive Cancer Network (NCCN) has not published any guidelines in support of the use of Adakveo (crizanlizumab) for the management of advanced glioblastoma, metastatic melanoma or GBM. One study is actively recruiting participants at the time of this review (NCT05909618).
- Myelofibrosis One phase Ib/2 study assessed the impact of ruxolitinib in combination with additional therapies (including Adakveo [crizanlizumab]) for the management of myelofibrosis. Only 6 of the 44 participants were exposed to Adakveo (crizanlizumab) and explicit outcomes for this combination were not published. High quality evidence is needed to support the safety and efficacy of Adakveo (crizanlizumab) for the management of myelofibrosis.
- Priapism. Only one small (n=36) study has assessed the use of Adakveo (crizanlizumab) for the management of priapism in those with SCD (SPARTAN - NCT03938454). There was no comparator group. A case series and a case report were published highlighting the potential benefit of Adakveo (crizanlizumab) for priapism in a total of 4 individuals. High quality evidence is needed to support the safety and efficacy of Adakveo (crizanlizumab) for the management of priapism.
- Retinal Vasculopathy Cerebral Leukoencephalopathy. There is one active study underway assessing the role of Adakveo (crizanlizumab) for retinal vasculopathy cerebral leukoencephalopathy (NCT04511880), and one clinical trial of 11 participants (no comparator group) found “promising potential” with the drug. High quality, large studies are needed to support the safety and efficacy of Adakveo (crizanlizumab) for retinal vasculopathy cerebral leukoencephalopathy.

Applicable Billing Codes

Table 1	
CPT/HCPCS codes considered experimental, investigational, unproven, 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

Table 2	
ICD-10 codes considered experimental, investigational, unproven, or not considered medically necessary with Table 1 (CPT/HCPCS) codes:	
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
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

Table 2	
ICD-10 codes considered experimental, investigational, unproven, or not considered medically necessary with Table 1 (CPT/HCPCS) codes:	
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

Table 2	
ICD-10 codes considered experimental, investigational, unproven, or not considered medically necessary with Table 1 (CPT/HCPCS) codes:	
D57.813	Other sickle-cell disorders with cerebral vascular involvement
D57.814	Other sickle-cell disorders with dactylitis
D57.818	Other sickle-cell disorders with crisis with other specified complications
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

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