Drug Monograph

Drug Name: **Adakveo® (crizanlizumab-tmca) injection**
Drug Class: **P-Selectin Inhibitor**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Adakveo is available as a single-dose vial containing 100 mg/10 ml (10 mg/ml) of crizanlizumab-tmca for intravenous injection.
Manufacturer:	Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936.
Summary of Findings:	The efficacy of Adakveo for the treatment of reduction in frequency of vasoocclusive crises (VOCs) was demonstrated in 198 patients receiving Adakveo or placebo. Patients with sickle cell disease who received Adakveo 5 mg/kg had a lower median annual rate of VOC compared to placebo-treated patients (1.63 vs 2.98; p=0.010, 95% CI). 36% of patients treated with Adakveo 5 mg/kg did not experience a VOC compared to 17% of placebo-treated patients. The median time to first VOC from randomization was 4.1 months in the Adakveo 5 mg/kg arm compared to 1.4 months in the placebo arm.
Status Recommendation:	☐ Clinical Edit ☒ PA Required ☐ Open Access ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Sickle cell disease (SCD) Is a rare genetic disorder that affects approximately 100,000 people in the US. Vasoocclusive crisis (VOCs), also known as acute sickle cell pain crisis, is a major complication of SCD. VOCs often occur multiple times a year and are the main reason for seeking treatment in SCD. VOCs are periodic episodes in which pain develops when sickle-shaped red blood cells block blood flow through tiny blood vessels to chest, abdomen, joints and bones. VOCs are considered a medical emergency, and are a frequent reason for emergency department visits and hospitalizations.

Dosage Form [3]

Adakveo is available as a single-dose vial containing 100 mg/10 ml (10 mg/ml) of crizanlizumab-tmca for intravenous injection.

Manufacturer [3]

Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936.

Indication(s) [3]

Adakveo is indicated to reduce the frequency of vasoocclusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Adakveo is a humanized IgG2 kappa monoclonal antibody that binds to P-selectin and blocks interactions with its ligands including P-selectin glycoprotein ligand 1.

Pharmacokinetics:

Volume of Distribution	4.26L
Metabolism	Metabolized into small peptides by catabolic pathways
Excretion	Clearance: 11.7 ml/hour in healthy volunteers
Half-life	10.6 days

Clinical Trials Experience
SUSTAIN Trial

STUDY 1 DESIGN	Randomized, multicenter, placebo-controlled, double-blind study (n = 198)
INCLUSION CRITERIA	• Sickle Cell Disease (HbSS, HbSC, HbSβ⁰-thalassemia, or HbSβ⁺-thalassemia) • If receiving hydroxyurea or erythropoietin, treatment must have been prescribed for at least 6 months, with the dose stable for at least 3 months • Between 2 and 10 sickle cell-related pain crises in the past 12 months
EXCLUSION CRITERIA	• On a chronic transfusion program or planning on exchange transfusion during the study • Hemoglobin < 4.0 g/dL • Planned initiation, termination, or dose alteration of hydroxyurea during the study • Receiving chronic anticoagulation therapy (e.g. warfarin, heparin) other than aspirin
TREATMENT REGIMEN	Patients were randomized to receive Adakveo (n=67) 5 mg/kg, Adakveo 2.5 mg/kg (n=66), or placebo (n=65) administered over a period of 30 minutes by intravenous infusion on Week 0, Week 2, and every 4 weeks thereafter for a treatment duration of 52 weeks.
RESULTS	The primary outcome measured was the rate of sickle cell-related pain crises over 1 year. Patients with sickle cell disease who received Adakveo 5 mg/kg had a lower median annual rate of VOC compared to placebo-treated patients (1.63 vs 2.98; p=0.010). 36% of patients treated with Adakveo 5 mg/kg did not experience a VOC compared to 17% of placebo-treated patients. The median time to first VOC from randomization was 4.1 months in the Adakveo 5 mg/kg arm compared to 1.4 months in the placebo arm.
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [3,4]

- None

Warnings and Precautions [3,4]

- Infusion-Related Reactions: Monitor patients for signs and symptoms of infusion-related reactions, which may include fever, chills, nausea, vomiting, fatigue, dizziness, pruritus, urticaria, sweating, shortness of breath or wheezing. Discontinue infusion for severe reactions.
- Laboratory Test Interference: Interference with automated platelet counts (platelet clumping) has been observed following administration with Adakveo, in particular when blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA).

Adverse Effects [3,4]

Most common, ≥ 10%	(n = 66) %
Nausea	18
Arthralgia	18
Back pain	15
Pyrexia	11

Drug Interactions [3,4]

- Laboratory Test Interference- Platelet Tests: Adakveo interferes with automated platelet counts (platelet clumping) in particular when blood samples are collected in tubes containing EDTA, which may lead to unevaluable or falsely decreased platelet counts. Run blood samples within 4 hours of blood collection or collect blood samples in tubes containing citrate. When needed, estimate platelet count via peripheral blood smear.

Dosage and Administration [3,4]

Administer Adakveo 5 mg/kg diluted solution by intravenous infusion over a period of 30 minutes at Week 0, Week 2, and every 4 weeks thereafter.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**
Crizanlizumab-tmca	Adakveo	Novartis	100 mg/10 ml vial	$2,357 per vial

** Wholesale Acquisition Cost

Conclusion

Adakveo, a selectin blocker, is indicated to reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease. The safety and efficacy of Adakveo was demonstrated in one randomized, double-blind, placebo-controlled trial (SUSTAIN) that enrolled 198 patients with SCD. This trial showed a statistically significant difference in the patients randomized to receive Adakveo 5 mg/kg in the reduction of rate of sickle cell-related pain crises over 1 year compared to placebo. The most common adverse reactions (> 10%) with Adakveo were nausea, arthralgia, back pain and pyrexia.

Recommendation

The MO Healthnet Division recommends prior authorization status for this product.

References

1) Vaso-Occlusive Crisis. Sickle Cell Disease News. https://sicklecellanemianews.com/vaso-occlusive-crisis/. Accessed January 13, 2020.
2) Sickle Cell Anemia. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/sickle-cell-anemia/symptoms-causes/syc-20355876. Accessed January 13, 2020.
3) Product Information: Adakveo® (crizanlizumab-tmca). 2019. Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936.
4) Adakveo: Drug Information. Lexi-Drugs. Wolters Kluwer Clinical Drug Information Inc.
5) SUSTAIN: A Phase II, Multicenter, Randomized, Placebo-Controlled, Double-Blind, 12-Month

Study to Assess Safety and Efficacy of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Sickle Cell-Related Pain Crises. NCT01895361. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/study/NCT01895361?term=01895361&draw=2&rank=1. Accessed January 13, 2020.

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