Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM021.1225	**HEMATOLOGICAL AGENTS** **ADAKVEO®** (crizanlizumab-tmca vial)
Effective Date: 2/1/2026	**Review/Revised Date**: 04/20, 10/20, 11/21, 10/22, 10/23, 10/24, 10/25 (JH)
Original Effective Date: 06/20	**P&T Committee Meeting Date**: 04/20, 04/20, 06/20, 12/20, 12/21, 12/22, 12/23, 12/24, 12/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initiation of therapy (new starts), all the following criteria must be met:
1. Confirmed medical history or diagnosis of sickle cell disease
2. Patient has experienced at least two sickle cell-related pain crises in the prior year. A pain crisis is defined as acute episode of pain with no medically determined cause other than a vaso-occlusive event that resulted in a medical facility visit and treatment with oral or parenteral narcotic agents or with a parenteral nonsteroidal anti-inflammatory drug.
3. Documentation that patient meets one of the following:
    a. Patient will continue taking hydroxyurea with the requested therapy and patient has been on a maximally tolerated dose of hydroxyurea for at least six months
    b. Patient has had a therapeutic failure of hydroxyurea despite use of a maximally tolerated dose for at least six months
    c. Patient has had an intolerance or contraindication to hydroxyurea (for many patients, myelosuppression is dose-dependent and reversible. Intolerance due to myelosuppression will only be considered if patient continues to experience myelosuppression despite dose adjustments)

For patients established on the requested agent within the previous year: Documentation that the number or severity of sickle cell-related pain crises has decreased from baseline

EXCLUSION CRITERIA:
Used in combination with L-glutamine (Endari)

AGE RESTRICTIONS:
Approved for patients 16 years of age and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a hematologist or a provider experienced with the treatment of sickle cell disease

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year

QUANTITY LIMIT:
Induction dose: 5 mg/kg at week 0 and week 2.
Maintenance dose: 5 mg/kg every 4 weeks.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Crizanlizumab (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. By binding to P-selectin, crizanlizumab inhibits interactions between endothelial cells, platelets, red blood cells, and leukocytes, which may

result in decreased platelet aggregation, maintenance of blood flow, and minimized sickle cell-related pain crises.

FDA APPROVED INDICATIONS:
To reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease.

POSITION STATEMENT:
Sickle cell disease (SCD) is a common genetic disease, affecting about 100,000 people in the United States, resulting in a shortened life span of about 50 years in severe subtypes, impaired quality-of-life, and increased healthcare utilization. The disease is characterized by chronic hemolytic anemia, vaso-occlusion, and progressive vascular injury affecting multiple organ systems. In patients with SCD, polymerization of deoxygenated hemoglobin leads to a cascade of pathologic events: erythrocyte sickling, vaso-occlusion, tissue ischemia, reperfusion injury, hemolysis, abnormal activation of inflammatory and oxidative pathways, endothelial dysfunction, increased oxidative stress, and activation of coagulation pathways. These abnormalities have acute and chronic clinical consequences across multiple organ systems, including acute pain episodes, chronic pain syndromes, acute chest syndrome, anemia, stroke and silent cerebral infarcts, cognitive dysfunction, pulmonary hypertension, and other clinical consequences. Vaso-occlusion leads to recurrent painful episodes (sickle cell crisis).

Hydroxyurea is a mainstay in the overall management of individuals with SCD, decreasing incidence of acute painful episodes, decreasing hospitalization rates, and prolonging survival. Recommendations for hydroxyurea per the 2014 NHLBI guidelines:

- All patients should be counseled on therapy
- Should be offered for all children nine months and older regardless of clinical severity
- Should be initiated in adults who meet any of the following:
    - Have three or more sickle cell–associated moderate to severe pain crises in 12 months
    - Have a history of severe or recurrent acute chest syndrome (ACS)
    - Have sickle cell– associated pain that interferes with daily activities and quality of life
    - Have severe symptomatic chronic anemia that interferes with daily activities or quality of life
- Should be stopped in pregnant and breastfeeding women

Myelosuppression is the major dose-liming toxicity with hydroxyurea. However, for most individuals, myelosuppression is predictable, dose-dependent, and reversible.

Myelosuppression is used to adjust hydroxyurea dosing and can be easily controlled as long as there is regular hematologic monitoring and dose reduction for severe neutropenia, anemia, or thrombocytopenia.

The FDA approval of crizanlizumab was based on the Phase 2 SUSTAIN trial, which was a 52 week, randomized, placebo-controlled, double-blind study in 198 patients with SCD. Patients were randomized crizanlizumab 5 mg/kg, crizanlizumab 2.5 mg/kg, or placebo. The primary endpoint was the annual rate of VOCs leading to a healthcare visit for pain medication. Acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility) were also considered to be VOC crisis events. Patients who received crizanlizumab 5 mg/kg had a lower median annual rate of VOC vs. patients who received placebo (1.63 vs. 2.98; $p = 0.010$). Based on this trial crizanlizumab may provide a benefit to patients by reducing acute pain crises. However, the long-term benefits of this therapy are currently unknown. Crizanlizumab does represent a new treatment option for a disease with limited therapies. It may be a reasonable option for those that are still having pain crises despite hydroxyurea use or for those that are not able to tolerate hydroxyurea.

In a follow up study, the randomized, Phase 3 STAND trial (NCT03814746) compared crizanlizumab at doses of 5mg/kg or 7.5mg/kg, versus placebo, in addition to standard of care in 254 patients ages 12 and older with SCD who had experienced at least two VOCs leading to a healthcare visit in the previous 12 months. Preliminary results showed no statistically significant difference between either dose of crizanlizumab and placebo on the primary endpoint of VOC events leading to a healthcare visit in the first year after patients entered the study. No new safety concerns were identified. Results indicated that patients treated with crizanlizumab had on average 2.5 painful crises with a subsequent healthcare visit over the first year of treatment, compared with 2.3 crises in the placebo group. In addition, the average number of crises requiring a healthcare visit or treatment at home was 4.7 with crizanlizumab compared with 3.9 with placebo.

While the Phase 3 STAND trial did not meet its primary endpoint, the author of the study pointed out that a few contributing factors that could have impacted results. The STAND study was conducted during the COVID-19 pandemic which resulted in marked reduction in health care access and non-compliance with follow-up. Additionally, the pandemic reduced patient exposure to infections as general populations were advised to stay indoors and practiced social distancing. The SUSTAIN trial was conducted in the USA, Brazil and Jamaica with majority of the population being Black or African American while the STAND trial had only 49% in over 21 countries. The varied patient demographics, genotypes, cultural practices,

and use of health-care facilities or management of pain across different countries could have contributed to the lack of efficacy findings.

As a result of the STAND trial, in May 2023, the European Medicine Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that Adakveo (crizanlizumab) should no longer be used to prevent painful crises in patients aged 16 years and older with sickle cell disease. This recommendation followed a review by the CHMP which concluded that the benefits of the medicine did not outweigh its risks.

BILLING GUIDELINES AND CODING:

HCPCS code	Coding Description	Brand Name
J0791	Injection, crizanlizumab-tmca, 5mg	Adakveo®
ADMINISTRATION◊		
96365	Ther/proph/diag iv inf init	
96413	Chemo iv infusion 1 hr	

*Coding Notes:
• The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
• HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as “medically unlikely edits” (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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