

## Novel Treatments for Sickle Cell Disease (Adakveo<sup>®</sup>)

**Policy # 00704**

Original Effective Date: 05/11/2020

Current Effective Date: 05/01/2025

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Note: L-Glutamine (Endari<sup>™</sup>) is addressed separately in medical policy 00604.*

### When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member’s contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider crizanlizumab (Adakveo<sup>®</sup>)<sup>‡</sup> for the treatment of sickle cell disease to be **eligible for coverage.\*\***

#### Patient Selection Criteria

Coverage eligibility for crizanlizumab (Adakveo) will be considered when the following criteria are met:

- **Initial:**
  - Patient has a diagnosis of sickle cell disease including, but not limited to, HbSS, HbSC, sickle beta<sup>0</sup> thalassemia, and sickle beta<sup>+</sup> thalassemia; AND
  - Patient is greater than or equal to 16 years of age; AND
  - Patient has experienced at least 2 vasoocclusive crises (defined as acute episodes of pain requiring a medical facility visit and treatment with oral or parenteral narcotic agents or a parenteral NSAID) in the past 12 months; AND  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility based on clinical trial data and will be denied as not medically necessary\*\* if not met.)*
  - Patient is currently adherent to hydroxyurea therapy and the dose has been stable for at least 3 months OR the patient has a history of treatment failure, intolerance, or contraindication to the use of hydroxyurea; AND  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility based on clinical trial data and will be denied as not medically necessary\*\* if not met.)*
  - Requested dose does not exceed 5 mg/kg at weeks 0, 2, and every 4 weeks thereafter.

## Novel Treatments for Sickle Cell Disease (Adakveo®)

Policy # 00704

Original Effective Date: 05/11/2020

Current Effective Date: 05/01/2025

- **Re-authorization:**

- Patient has received an initial authorization for Adakveo; AND
- Patient is deriving benefit from treatment with Adakveo as is evidenced by a reduction in number of vasoocclusive crises; AND  
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary\*\* if not met.)*
- Patient is not receiving concomitant voxelotor (Oxbryta) therapy; AND
- Requested dose does not exceed 5 mg/kg every 4 weeks.

### **When Services Are Considered Not Medically Necessary**

Based on review of available data, the Company considers the use of crizanlizumab (Adakveo) when the patient has not experienced at least 2 vasoocclusive crises in the past year, or is not currently adherent or unable to tolerate a stable dose of hydroxyurea to be **not medically necessary.\*\***

Based on review of available data, the Company considers the continued use of crizanlizumab (Adakveo) when the patient has not experienced a reduction in vasoocclusive crises during treatment to be **not medically necessary.\*\***

### **When Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers the use of crizanlizumab (Adakveo) when patient selection criteria are not met (except those denoted as **not medically necessary\*\***) to be **investigational.\***

### **Background/Overview**

Adakveo is a monoclonal antibody indicated to reduce the frequency of vasoocclusive crises (VOCs) in patients  $\geq 16$  years of age. It works by binding to P-selectin, an adhesion molecule expressed on the surface of the endothelium. By binding to this molecule, the drug is thought to prevent the adhesion of sickled red blood cells to the surface of blood vessels and thus prevent vascular obstruction, VOCs, and inflammation. It is dosed intravenously at 5 mg/kg administered on week 0, week 2, and once every 4 weeks thereafter. Adakveo was specifically studied to reduce the number of VOCs experienced by patients with a history of at least 2 VOCs in the previous 12 months. It appears to be well-tolerated with the most common adverse events reported in the clinical trial being nausea, arthralgia, back pain, and pyrexia.

#### **Sickle Cell Disease**

Sickle cell disease is a group of inherited red blood cell disorders in which the hemoglobin is abnormal and leads to “sickling” of the red blood cells. This reduces the ability of the blood to transport oxygen to the body and can result in blocked blood vessels and tissue ischemia which manifest as various complications. Complications of sickle cell disease include acute VOCs, severe

## Novel Treatments for Sickle Cell Disease (Adakveo®)

Policy # 00704

Original Effective Date: 05/11/2020

Current Effective Date: 05/01/2025

anemia, splenic sequestration, acute chest syndrome, stroke, retinal damage, priapism, joint problems, and others. Patients with sickle cell disease have a shorter life expectancy than race-matched peers and often have a low quality of life due to frequent crises. Current pharmacologic treatment options for sickle cell disease include hydroxyurea (Droxia®, Siklos®, Hydrea®)‡, L-glutamine (Endari), and crizanlizumab (Adakveo). The most recent National Institutes of Health-National Heart, Lung, and Blood Institute Evidence-based management of sickle cell disease guidelines were published in 2014 and do not include Endari, or Adakveo. These guidelines note that only hydroxyurea and chronic blood transfusions are proven to be disease-modifying treatments for this condition. They recommend hydroxyurea therapy in adult patients in the following categories:

1. Who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period, or
2. Who have sickle-cell associated pain that interferes with daily activities and quality of life, or
3. Who have severe and/or recurrent acute chest syndrome, or
4. Who have severe symptomatic chronic anemia.

The guidelines also recommend hydroxyurea for infants  $\geq$  9 months of age, children, and adolescents with sickle cell anemia to reduce complications.

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

Adakveo was approved in November 2019 to reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease.

## **Rationale/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Adakveo was evaluated in patients with sickle cell disease in SUSTAIN, a 52-week, randomized, multicenter, placebo-controlled, double-blind study in 198 patients. Included patients had any sickle cell genotype (HbSS, HbSC, HbS/beta<sup>0</sup> thalassemia, HbS/beta<sup>+</sup> thalassemia, and others) and a history of 2-10 VOCs in the previous 12 months. Patients were randomized 1:1:1 to Adakveo 5 mg/kg (n=67), Adakveo 2.5 mg/kg (n=66), or placebo (n=65). Infusions were 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. Randomization was stratified by patients already receiving hydroxyurea and by the number of VOCs in the previous 12 months. Patients received Adakveo (with or without hydroxyurea) and were allowed to receive occasional transfusions and pain medications as needed.

## Novel Treatments for Sickle Cell Disease (Adakveo®)

Policy # 00704

Original Effective Date: 05/11/2020

Current Effective Date: 05/01/2025

Efficacy was evaluated in the SUSTAIN study by the annual rate of VOCs leading to a healthcare visit. A VOC leading to a healthcare visit was defined as an acute episode of pain with no cause other than a vasoocclusive event that required a medical facility visit and treatment with oral or parenteral opioids, or parenteral NSAIDs. Acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility) were also considered VOCs.

Patients receiving Adakveo 5 mg/kg had a lower median annual rate of VOC compared to patients who received placebo (1.63 vs 2.98) which was statistically significant ( $p=0.01$ ). Reductions in the frequency of VOCs were observed among patients regardless of sickle cell disease genotype and/or hydroxyurea use.

### **References**

1. Adakveo [package insert]. Novartis Pharmaceuticals Corporation. East Hanover, New Jersey. Updated November 2019.
2. Adakveo Drug Evaluation. Express Scripts. Updated December 2019.
3. Hydroxyurea use in sickle cell disease. UpToDate. Updated January 2020.
4. The National Institutes of Health—National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease, Expert Panel Report 2014. Available at: [https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816\\_0.pdf](https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf).

### **Policy History**

Original Effective Date: 05/11/2020

Current Effective Date: 05/01/2025

04/02/2020	Medical Policy Committee review
04/08/2020	Medical Policy Implementation Committee approval. New policy.
04/01/2021	Medical Policy Committee review
04/14/2021	Medical Policy Implementation Committee approval. No change to coverage.
04/07/2022	Medical Policy Committee review
04/13/2022	Medical Policy Implementation Committee approval. Updated Oxbryta criteria and background information to reflect FDA approval for patients aged 4 years and older.
04/06/2023	Medical Policy Committee review
04/12/2023	Medical Policy Implementation Committee approval. Updated Oxbryta criteria to allow for patients younger than 12 years of age with no prior VOCs to be eligible based on clinical trial inclusion criteria. Added criteria restricting new 300 mg tablet and 300 mg tablet for oral suspension dosage forms to pediatric patients weighing less than 40 kg.
04/04/2024	Medical Policy Committee review
04/10/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged

## Novel Treatments for Sickle Cell Disease (Adakveo®)

Policy # 00704

Original Effective Date: 05/11/2020

Current Effective Date: 05/01/2025

04/03/2025 Medical Policy Committee review

04/09/2025 Medical Policy Implementation Committee approval. Removed Oxbryta from policy since it has been removed from the market. Title changed from “Novel Treatments for Sickle Cell Disease (Adakveo, Oxbryta)” to “Novel Treatments for Sickle Cell Disease (Adakveo).”

Next Scheduled Review Date: 04/2026

### **Coding**

*The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

*The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Louisiana Blue Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.*

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J0791 Delete codes effective 05/01/2025: C9399, J3490, J3590
ICD-10 Diagnosis	All Related Diagnoses

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and

Novel Treatments for Sickle Cell Disease (Adakveo®)

Policy # 00704

Original Effective Date: 05/11/2020

Current Effective Date: 05/01/2025

whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
1. Consultation with technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

**\*\*Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

**NOTICE:** Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.