Endari (L-glutamine)
Prior Authorization Program Summary

POLICY REVIEW CYCLE

Effective Date	Date of Origin
10-01-2024	

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Endari®* (L-glutamine) Oral powder *generic available	To reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Sickle Cell Disease	Sickle cell disease (SCD) is the name given to a group of lifelong inherited conditions that affect hemoglobin. People with SCD have atypical hemoglobin molecules called hemoglobin S, which can distort red blood cells into a sickle or crescent shape.(2) Signs and symptoms of SCD usually begin in early childhood. Characteristic features of SCD include anemia, repeated infections, and periodic episodes of pain. The severity of symptoms varies from person to person and can range from mild to requiring frequent hospitalizations.(2) SCD affects nearly every system in the body. SCD has both acute and chronic complications. An episode of severe pain [acute vaso-occlusive crisis (VOC)] is the most common acute complication of SCD. In addition to VOCs, other common acute complications of SCD include fever related to infection, acute kidney injury (AKI), hepatobiliary complications, acute anemia, splenic sequestration, acute chest syndrome (ACS), and acute stroke. Chronic complications of SCD can affect almost any organ, and certain acute complications often evolve into chronic phases. The most common chronic complications of SCD include chronic pain, chronic anemia, avascular necrosis, leg ulcers, pulmonary hypertension, renal complications, stuttering/recurrent priapism, and ophthalmologic complications.(2) Pain is the most common complication of SCD for both acute and chronic complications. Pain can be acute, chronic, or an acute episode superimposed on chronic pain. In SCD, pain is considered chronic if it lasts more than 3 months. People with SCD experience both nociceptive and neuropathic pain.(2) Recurrent and unpredictable episodes of vaso-occlusion are the hallmark of sickle cell disease. Discoveries over the past 2 decades have highlighted the important contributions of various cellular and soluble participants in the vaso-occlusive cascade. Although the molecular basis of SCD is well characterized, the complex mechanisms underlying VOC have not been fully elucidated. Based on direct observations in SCD mice, adhesive interactions of SS-RBCs and leukocytes to the endothelium play

	important roles in the initiation of VOC. It is thought that the activated adherent leukocytes, which are rigid and larger than sickle cell-red blood cells (SS-RBC), likely drive VOC in collecting venules, whereas the SS-RBCs may contribute in smaller vessels or in situations where there is no potent inflammatory trigger.(4) Triggers for VOC vary and can include inflammation, stress, increased viscosity, decreased flow, hemolysis, or a combination of the following factors:(4) • Endothelial activation by SS-RBCs and other inflammatory mediators • Recruitment of adherent leukocytes • Activation of recruited neutrophils and of other leukocytes (e.g., monocytes or iNKT cells) • Interactions of sickle erythrocytes with adherent neutrophils • Vascular clogging by heterotypic cell-cell aggregates composed of SS-RBCs, adherent leukocytes and possibly platelets • Increased transit time to greater than the delay time for deoxygenation-induced hemoglobin polymerization, propagating retrograde VOC • Ischemia as a result of the obstruction that creates a feedback loop of worsening endothelial activation Sickle hemoglobin can cause damage to the RBC membrane from deformation by polymer formation. In addition, the mutated globin can undergo autooxidation and precipitate on the inner surface of the RBC membrane, causing membrane damage via iron-mediated generation of oxidants. Both endothelial selectins, P-selectin and E-selectin, have been suggested to participate in VOC.(4) Nearly all people with SCD have chronic anemia, but individual baseline hemoglobin values vary widely depending upon hemoglobin genotype (HbSS, HbSC, HbSβ^+-thalassemia, HbSβ^0-thalassemia). It is important for the patient and the primary care provider to know the baseline or "steady state" hemoglobin value to inform ongoing monitoring and management during acute complications.(2) Hydroxyurea, a ribonucleotide reductase inhibitor, was identified as an option to increase fetal hemoglobin (HbF) levels in people with SCD. The initial clinical trial of hydroxyurea for the treatment of sickle cell anemia (SCA) involved two people. The results of this study showed favorable outcomes which lead to two extended studies with larger cohorts of people. Although HbF induction is the most powerful effect of hydroxyurea and provides the biggest direct benefit for people who have SCD, additional mechanisms of actions and benefits exist. Hydroxyurea lowers the number of circulating leukocytes and reticulocytes and alters the expression of adhesion molecules, all of which contribute to vaso-occlusion. Hydroxyurea also raises RBC volume [higher mean corpuscular volume (MCV)] and improves cellular deformability and rheology, which increases blood flow and reduces vaso-occlusion.(3) An expert panel report of evidence-based management of sickle cell disease supports the use of hydroxyurea with strong recommendations in the following:(3) • In adults with SCA who have three or more sickle cell-associated moderate to severe pain crises in a 12 month period • In adults with SCA who have sickle cell-associated pain that interferes with daily activity and quality of life • In adults with SCA who have a history of severe and/or recurrent acute coronary syndrome (ACS) • In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life • In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce SCD-related complications (e.g., pain, dactylitis, ACS, anemia)

	A clinical response to treatment with hydroxyurea may take 3-6 months. Therefore, the expert panel report of evidence-based management of sickle cell disease recommends a 6 month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.(3) While hydroxyurea remains the first-line therapy for SCD, L-glutamine, crizanlizumab, and voxelotor have been approved as adjunctive or second-line treatments, and hematopoietic stem cell transplant with a matched sibling donor is now standard care for severe disease. The emergence of gene therapies for SCD now bring the potential for curative therapy without a matched donor.(5)
Efficacy	The mechanism of action of the amino acid L-glutamine in treating sickle cell disease (SCD) is not fully understood. Oxidative stress phenomena are involved in the pathophysiology of SCD. Sickle red blood cells (RBCs) are more susceptible to oxidative damage than normal RBCs, which may contribute to the chronic hemolysis and vaso-occlusive events associated with SCD. The pyridine nucleotides, NAD+ (oxidized nicotinamide adenine dinucleotide) and its reduced form NADH (nicotinamide adenine dinucleotide + hydrogen), play roles in regulating and preventing oxidative damage in RBCs. L-glutamine may improve the NAD redox potential in sickle RBCs through increasing the availability of reduced glutathione.(1) The efficacy of L-glutamine was evaluated in a randomized, double-blind, placebo controlled, multi-center clinical trial. The trial evaluated 230 patients with SCD who had 2 or more painful crises within the 12 months prior to enrollment. Eligible patients stabilized on hydroxyurea for at least 3 months continued their therapy throughout the study. Efficacy was demonstrated by a reduction in the number of sickle cell crises through Week 48 and prior to the start of tapering among patients that received L-glutamine compared to patients who received placebo. The recurrent crisis event time analysis yielded an intensity rate ratio (IRR) value of 0.75 with 95% CI= (0.62, 0.90) and (0.55, 1.01) based on unstratified models using the Andersen-Gill and Lin, Wei, Yang and Ying methods, respectively in favor of L-glutamine, suggesting that over the entire 48-week period, the average cumulative crisis count was reduced by 25% from the L-glutamine group over the placebo group.(1)
Safety	Endari (L-glutamine) has no FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	Endari prescribing information. Emmaus Medical, Inc. October 2020.
2	U.S. National Library of Medicine. Genetics Home Reference. Sickle cell disease. November 2019.
3	U.S. Department of Health and Human Services. National Institute of Health. Evidence-Based Management of Sickle Cell Disease. Expert Panel Report, 2014.
4	Manwani D, Frenette PS, Vaso-occlusion in sickle cell disease: pathophysiology and novel targeted therapies. Blood. 2013 Dec 5; 122(24): 3892-3898.
5	Brandow AM, Liem RI. Advances in the diagnosis and treatment of sickle cell disease. Journal of Hematology & Oncology. 2022;15(1). doi:10.1186/s13045-022-01237-z.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Endari	glutamine (sickle cell) powd pack	5 GM	M ; N ; O ; Y	O ; Y		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Endari	glutamine (sickle cell) powd pack	5 GM	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of sickle cell disease **AND** 2. The patient is using the requested agent to reduce the acute complications of sickle cell disease **AND** 3. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 4. ONE of the following A. The patient has tried and had an inadequate response after at least 6 months duration of therapy with maximally tolerated hydroxyurea **OR** B. The patient has an intolerance or hypersensitivity to hydroxyurea **OR** C. The patient has an FDA labeled contraindication to hydroxyurea **AND** 5. ONE of the following: A. The patient will NOT be using the requested agent in combination with Adakveo (crizanlizumab-tmca) OR Oxbryta (voxelotor) for the requested indication **OR** B. There is support for use of the requested agent in combination with Adakveo (crizanlizumab-tmca) or Oxbryta (voxelotor) for the requested indication **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 7. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **Length of Approval:** 12 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent (i.e., reduction in acute complications of sickle cell disease since initiating therapy with the requested agent) **AND** 3. ONE of the following: A. The patient will NOT be using the requested agent in combination with Adakveo (crizanlizumab-tmca) OR Oxbryta (voxelotor) for the requested indication **OR** B. There is support for use of the requested agent in combination with Adakevo (crizanlizumab-tmca) or Oxbryta (voxelotor) for the requested indication **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **Length of Approval:** 12 months

