VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Endari™ (L-glutamine oral powder – Emmaus Medical, Inc)

TAC APPROVAL DATE: 10/17/2018

OVERVIEW

Endari is indicated to reduce the acute complications of sickle cell disease (SCD) in adults and pediatric patients ≥ 5 years of age.[1]

L-glutamine is an essential amino acid and serves as a precursor of nucleic acids and nucleotides including the pyridine nucleotides (nicotinamide adenine dinucleotide [NAD] and reduced nicotinamide adenine dinucleotide [NADH]).[1,2] These pyridine nucleotides play key roles in the regulation and prevention of oxidative damage in red blood cells (RBCs) and studies have shown that oxidative phenomena may play a significant role in the pathophysiology of SCD.

Disease Overview

SCD, a multisystem disorder, is the most common condition caused by a single gene mutation.[3] In the US, population estimates suggest that a total of 100,000 persons have the disease. Approximately 300,000 babies are born with sickle cell anemia each year and it is estimated that the number could be as high as 400,000 by 2050. The prevalence of the disease is high throughout large areas in sub-Saharan Africa, the Mediterranean basin, the Middle East, and India because of the remarkable level of protection that the sickle cell trait provides against severe malaria. The exact mechanism of protection is still being debated; however, the "malaria hypothesis" is an example of natural selection and balanced polymorphism.

SCD is characterized by the presence of abnormal erythrocytes damaged by the sickle hemoglobin (HbS) gene – this variant of the normal adult hemoglobin (HbA) can be inherited from both parents or from one parent along with another variant, such as hemoglobin C (HbC) or with β-thalassemia.[3] Complications of SCD include vaso-occlusion (which can result in pain and organ failure), hemolytic anemia, and large-vessel vasculopathy (cerebrovascular disease, pulmonary hypertension, ischemic organ damage [hyposplenism, renal failure, bone disease, liver failure).

Guidelines

The National Institutes of Health (NIH) – National Heart, Lung, and Blood Institute issued the Evidence-Based Management of SCD, Expert Panel Report in 2014.[7] The report notes that there are only two currently proven disease-modifying treatments for patients with SCD: hydroxyurea and chronic blood transfusions. The use of L-glutamine in SCD is not mentioned; guidelines were published before the approval of Siklos® (hydroxyurea tablets). Hydroxyurea therapy is recommended in adult patients with sickle cell anemia with the following characteristics (strong recommendations): those with three or more sickle cell-associated moderate to severe pain crises in a 12-month period; those who have sickle cell-associated pain that interferes with daily activities and quality of life; patients with a history of severe and/or recurrent acute chest syndrome; and patients who have severe symptomatic chronic anemia that interferes with daily activities or quality of life. Hydroxyurea is also recommended in adults and children with SCD who have chronic kidney disease and are taking erythropoietin (weak recommendation). Hydroxyurea therapy should be offered to infants ≥ 9 months of age, children, and adolescents with sickle cell anemia to reduce SCD-related complications (e.g. pain, dactylitis, acute chest syndrome, anemia). Discontinue therapy in pregnant or breastfeeding patients. Laboratory monitoring is recommended before initiation of

therapy and during therapy (e.g., complete blood count with white blood cell differential, reticulocyte count, platelet count, RBC mean corpuscular volume). Clinical response to hydroxyurea therapy may take 3 to 6 months; a 6-month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure. Long-term hydroxyurea therapy is indicated in patients with clinical response.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Endari. Because of the specialized skills required for evaluation and diagnosis of patients treated with Endari as well as the monitoring required for adverse events, approval requires Endari to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 1 year in duration unless otherwise noted below.

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and/or laboratory data. Subsequent coverage reviews for a patient who has previously met the documentation requirements and related criteria in the *ESI Endari Prior Authorization Policy* through the ESI Coverage Review Department, and who is now requesting reauthorization, the criteria utilized do NOT require resubmission of documentation for reauthorization.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Endari is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Sickle Cell Disease (SCD) [documentation required].**
   - **A)** Approve Endari for 1 year if the patient meets all of the following criteria (i and ii):
     - **i.** The patient is ≥ 5 years of age; AND
     - **ii.** Endari is prescribed by, or in consultation with, a physician who specializes in SCD (e.g., a hematologist).

   Endari is indicated to reduce the acute complications of sickle cell disease (SCD) in adults and pediatric patients ≥ 5 years of age.[1]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Endari has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for conditions not included in the Recommended Authorization Criteria.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Endari™ oral powder [prescribing information]. Torrance CA: Emmaus Medical, Inc; July 2017.

2. FDA Briefing document, Oncologic Drugs Advisory Committee Meeting: L-glutamine. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM559734.pdf. Accessed on October 10, 2018.
3. Piel FB, Steinberg MH. Sickle cell disease. *N Engl J Med*. 2017;376:1561-1573.
4. Azar S, Wong TE. Sickle cell disease – a brief update. *Med Clin North Am*. 2017;101:375-393.
5. Droxia® capsules [prescribing information]. Princeton NJ: Bristol-Myers Squibb; March 2016.
6. Siklos™ tablets [prescribing information]. Bryn Mawr PA: Medunik USA, Inc; December 2017.
7. The National Institutes of Health – National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease, Expert Panel Report 2014. Available at: http://www.nhlbi.nih.gov/guidelines. Accessed on October 10, 2018.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	---	10/04/2017
Selected Revision	Trial of at least two OTC single-entity glutamine dietary supplement formulations is not needed for approval.	11/15/2017
Selected Revision	Added "documentation required" for the sickle cell disease diagnosis.	04/18/2018
Annual revision	No criteria changes.	10/17/2018

TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx.